Remarks

The Specification

Substitute specifications were filed November 3, 2004 and February 10, 2005. A description of the amendments made to the specification was listed in the Request to File Substitute Specification filed February 10, 2005. However, in consideration of the Examiner's confusion and since these substitute specifications have not been entered, the amendments to the specification have been made as described above pursuant to 37 C.F.R. § 1.121. These amendments correspond to the substitute specification filed February 10, 2005.

The specification has been amended pursuant to 37 C.F.R. § 1.77 to include the appropriate section headers, "Background of the Invention," "Brief Summary of the Invention," "Detailed Description of the Invention," and "Brief Description of the Drawings."

Original Figures 1, 4 and 5 have been deleted and the remaining figures renumbered appropriately. Figure 1 has been converted to Table 1 and the specification has been amended to incorporate Table 1 at page 28, line 23. Table 1 now correctly recites "NA nmol/l." NA as originally listed in Figure 1, now Table 1, is noradrenline. The specification has also been amended to delete all references to original Figures 1, 4 and 5.

Please replace original Figures 2 and 3 with the replacement sheets submitted herewith as renumbered Figures 1 and 2, respectively. The specification has been amended to refer to newly renumbered Figures 1 and 2 as appropriate. Specifically, the specification has been amended to refer to Figures 1 and 2, which were originally described in the specification on pages 20 and 21, under the section heading "Brief Description of the Drawings."

The specification has been amended to delete Examples 6-9 on pages 38-47. The specification has also been amended to renumber Examples 10-12 as Examples 6-8. The Examiner objected to the deletion of these Examples under 35 U.S.C. § 132(a) for **addition** of new matter. Contrary to the Examiner's assertion, the deletion of these examples does not contain new matter and does not change the scope of the application in any way. 35 U.S.C. § 132 (a) states that "no amendment shall **introduce** new matter into the disclosure of the invention." Furthermore the MPEP states that "35 U.S.C. 132 should be employed as a basis for objection to amendments to the abstract, specification, or drawings **attempting to add new** disclosure to that originally disclosed on filing." The Applicants have **not introduced or added** matter into the specification. They have deleted matter from the specification. Therefore, the objection to the specification for deletion of subject matter is moot.

Objections to the Drawings

Replacement sheets are filed herewith for original Figures 2 and 3, renumbered as Figures 1 and 2, respectively. The Examiner objected to new Figure 1 (original Figure 2) because the Y axis is not labeled. The Y axis of Figure 1 now recites "NA nmol/l." The Examiner also objected to new Figure 2 (original Figure 3) because the Y axis was labeled as "cell mean" and not "aldosterone ng/ml." The Y axis of Figure 2 now recites "aldosterone ng/ml."

Rejection Under 35 U.S.C. § 112, first paragraph, enablement

Claims 1-4, 19 and 29-31 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Examiner is correct in noting that the claims did not recite "cachexia." Applicants wish to note that cachexia is clearly defined as "weight loss due to underlying disease" in the specification at least at page 1, lines 3-5, lines 7-8 and page 4, lines 2-3. While applicants feel that "weight loss due to underlying disease" as previously recited in the claims would be clearly understood by one of ordinary skill in the art to mean cachexia, the claims have been amended to refer to a method of treating cachexia to avoid confusion.

The quantity of experimentation necessary for treating cachexia in a patient by administering an effective amount of an agent which reduces sympathetic nervous system activity is **not undue.** Applicants submit that a common mechanism (i.e. increased SNS activity) leads to cachexia in a number of patients with different diseases. Therefore, cachexia can be treated with drugs that are functionally-related by their ability to decrease SNS activity. See Table 1, previously Figure 1, in this respect.

One of ordinary skill in the art will be experienced in selecting and adjusting doses for a particular patient. Many known and approved drugs are available for use, ***now that the mechanism for treatment of cachexia is known.*** Therefore, one of ordinary skill in the art would also clearly be able to assess compatibility of the compound selected to treat cachexia with any other medications that the patient is taking based on information available to one of

skill in the art. It is not necessary for applicants to explain drug compatibility in the specification, as this is something that the skill person already assesses routinely on a patient-by-patient basis, based on standard reference sources, taking into account all the medications a patient is taking. The need to take into account all the medications a patient is taking is obvious and applies to **any** therapeutic regime. The test as affirmed by the Courts and the Board of Appeals has consistently been that one does not have to give every detail a health care provider would need, so long as sufficient detail was provided to enable the health care provider to practice the claimed method.

Applicants have demonstrated that **common features** are shared by cachexia patients arising from a wide range of different underlying conditions. On page 27, line 25 to page 28, line 9, the specification describes how cachexia relates to sympathetic nervous system activity and refers to Table 1 and Figure 1 (original Figures 1 and 2), which demonstrate that patients with weight loss due to a number of diseases have elevated noradrenaline plasma levels (i.e. SNS activity) compared to controls. Accordingly, the Applicants have found that cachectic patients with a range of underlying diseases show a similar hormonal profile, and have described how to treat the weight loss with the agents listed on page 4, line 10 to page 13, line 22. Therefore, the compounds as defined by the claims and disclosed in the specification should be effective in treating cachexia regardless of the nature of the underlying disease.

Example 11, pages 53-55, discloses treatment of cachexia with carvedilol. Page 55, line 15 states that "beta-blocker treatment was beneficial in a cachectic patient." Example 12

discloses treatment of a cachexia patient with an aldosterone antagonist. Page 57, lines 14-15, discloses that aldosterone antagonist treatment was beneficial in a cachectic patient.

Applicants have further demonstrated a beneficial effect on cachexia following treatment with beta receptor blockers. The Examiner is directed to the enclosed abstract by Anker, et al. entitled "The impact of body mass index and body weight changes on prognosis in patients with chronic heart failure: results of the COMET study" which has been accepted for publication in Circulation at the end of October in the abstract supplement for the American Heart Association meeting taking place in November 2005.

A Declaration Under 37 C.F.R. § 1.132 being submitted under separate cover provides additional examples that demonstrate enablement of the method as defined by the claims and described in the application as filed. The Declaration provides evidence of experiments conducted according to the guidance in the specification that demonstrate the beneficial effects on cachexia following treatment with beta receptor blockers, erythropoietin analogues and aldosterone antagonists. For example, the declaration describes that the inventors confidentially requested a colleague treat patients with cachexia due to cancer, a non-cardiovascular illness, with beta-blockers and spironolactone. The results from these experiments provided in the declaration demonstrate that cachexia was effectively treated with beta-blockers and spironolactone.

It is clear from the amount of direction and guidance presented in the specification, the state of the prior art, the relative skill of those in the art, that one of ordinary skill in the art could and did (as evidenced by the Declaration) use an agent which reduces sympathetic nervous

system activity to treat cachexia in a patient, as defined by the claims. Therefore, claims 1-4, 19 and 29-31 are enabled by the specification.

Rejection Under 35 U.S.C. § 112, first paragraph, written description

Claims 1-4 and 19 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The written description requirement for a claimed genus may be satisfied through a sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or a disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

The Examiner argues on page 9 of the office action that the claims fail to meet the written description requirement because "all possible" compounds that reduce SNS activity are not disclosed.

There is no legal requirement that applicants disclose all possible compounds that reduce SNS. Applicants have described the critical mechanism for treatment, the general class of compounds which are effective, and provided a number of representative species. Applicants

also demonstrated that a number of these representative species were effective in treating cachexia resulting from widely disparate diseases. ***This meets the legal requirements.***

Applicants have provided numerous species in the specification at least at page 4, line 10 to page 8, line 6 that reduce SNS activity. Furthermore, the representative number of species may be described by functional characteristic coupled with a **known** correlation between function and structure. The Applicants have discovered that a common mechanism (i.e. increased SNS activity) leads to cachexia in a number of patients with different diseases. Applicants have demonstrated as acknowledged by the Examiner on page 7 of the office action that patients with cachexia and increased SNS activity have elevated levels of aldosterone, noradrenaline and catecholamines (see pages 27, lines 12-15, page 28, lines 1-2, and page 29, lines 7-9, respectively). The Applicants have discovered that compounds falling within particular therapeutic classes, well known to one of ordinary skill in the art, are useful in treating cachexia by altering SNS activity through affecting the levels of these molecules. For example, the specification at least at example 11, pages 53-55, demonstrates that carvedilol, whose function (i.e. affects catecholamine levels) and structure are well known to one of ordinary skill in the art, is effective in treating a patient with cachexia. Additional compounds known to one of ordinary skill in the art that affect aldosterone, noradrenaline and catecholamine levels are described in the specification at least at page 4, line 10 to page 8, line 6. In addition, page 8, line to page 13, line 22, the specification further discloses publications in which many of the compounds are described in detail. As acknowledged by the Examiner it is not necessary to provide information well known to one of ordinary skill in the art.

The Applicants have clearly met the written description requirement by providing a description of a large number of species of compounds that have the functional characteristic required by the claims, whose structures are well known to one of ordinary skill in the art. Therefore, claims 1-4 and 19 satisfy the written description requirement.

Rejection Under 35 U.S.C. § 102

Claims 1-4, 19 and 29-31 were rejected under 35 U.S.C. § 102(b) as being anticipated by The RALES investigators, "Effectiveness of *Spironolactone* added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (The Randomized Aldactone Evaluation Study [RALES])" *The American Journal of Cardiology* 78:902-907 (1996). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

As discussed above, claim 1 was amended to define a method of treating cachexia. The population treated with spironolactone in the RALES study is **not** the same population as specified in the claims as amended. RALES describes treating patients with chronic heart failure with spironolactone. RALES does not disclose or suggest selecting patients with cachexia, nor does it disclose that patients treated with spirolactone experienced weight gain.

In contrast to RALES, the method as defined by the claims relates to treatment of patients with cachexia. The claims do not define treatment of cachexia **candidates**. The claims as amended require selection of the patient on the basis of cachexia. As previously noted, not all patients with heart failure have cachexia (see page 27, lines 15-16; see also the enclosed copy of Hunt, et al., "ACC/AHA guidelines for the evaluation and management of chronic heart failure

in the adult: executive summary" *Journal of the American College of Cardiology* 38:7 (2102-2113 (2001) page 2109, first column).

Applicants describe in the specification at least at page 40, lines 3-5 in Example 4, that "patients with chronic heart failure who developed cardiac cachexia demonstrate particularly abnormal reflex control within the cardiovascular and respiratory systems." Therefore, cachexia is not merely a reflection of the underlying disease state, but is linked with particular parameters, not previously recognized.

As shown in the enclosed reference by Florea, et al., *Int. J. Cardiol.* 97:15-20 (2004) and Florea, et al., *American Heart J.* 144(1):45-50 (2002), there is no difference in cardiac function (as seen by either echocardiography or MRI) between patients with or without cachexia. For example the first paragraph of the Discussion of page 48 in Florea, et al., (2002), states that "the current study failed to detect any specific cardiac abnormalities in patients with cachectic CHF compared with patients with non-cachectic CHF when assessed in a cross-sectional study." Therefore, one of ordinary skill in the art would not consider that treatment of cardiac function would necessarily treat cachexia.

Additional treatments of heart failure (for example, diuretics, LV assist devices) with similar efficacy to, for example, beta receptor blockers, **do not** lead to weight gain, but instead weight loss, due to water loss. For example, see the enclosed reference by Clark, et al., *Eur. Heart J.* 22(24):2275-2283 (2001), which shows that another treatment for heart failure, use of a ventricular assist device, that improves patients' conditions, is not associated with weight gain.

It is also well known to one of ordinary skill in the art that diuretics (other than aldosteron antagonists) are an effective treatment for heart failure, and it is also well known that they do not improve cachexia and therefore are not useful for cachexia.

Weight loss is a sign of successful heart failure (HF) treatment when diuretics are used. The enclosed copy of Niebauer, et al., *Lancet* 353:1838-1842 (1999) illustrates the effect of diuretics. For example, page 1840, second paragraph of second column discloses that "intensive diuretic treatment for a mean 23 days (8) in ten patients with chronic heart failure resulted in a mean weight decrease of 3.6 kg (range 2.5-5.0), and improvement in the functional NYHA class in nine of ten patients." One of ordinary skill in the art would consider that diuretics produce weight loss when given to patients with heart failure. The use of diuretics as treatment in HF is indicated as per guidelines for HF therapy of the European Societyof Cardiology as well as the American Heart Association and American College of Cardiology (see for example page 2108 of the enclosed reference Hunt, et al., "ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary" *Journal of the American College of Cardiology* 38:7 (2102-2113 (2001); the European Society of Cardiology Guidelines, Remme and Swedberg, "Comprehensive guidelines for the diagnosis and treatment of chronic heart failure. Task force for the diagnosis and treatment of chronic heart failure of the European Society of Cardiology" *European Journal of Heart Failure* 4:11-22 (2002) and Faris, et al., *Int. J. Cardiol.* 82:149-158 (2002). Therefore, treating and improving the underlying disease does not automatically lead to improvement in cachexia. The claims of the present application

disclose treatments for cachexia that are not dependent upon treatment of the symptoms of the underlying disease.

RALES does not disclose or suggest selecting patients with cachexia, nor does it disclose that patients treated with spirolactone exprienced weight gain. Therefore, claims 1-4, 19 and 29-31 are not anticipated by RALES.

Allowance of claims 1-27 and 29-31 is respectfully solicited.

Respectfully submitted,

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Abstract accepted for publication in Circulation

The impact of body mass index and body weight changes on prognosis in patients with chronic heart failure: results of the COMET study.

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The long-term impact of low body mass index (BMI) and weight loss in patients with chronic heart failure (CHF) treated with ACE inhibitors and beta blockers is not known. There is no data on the prognostic value of weight gain in CHF.
Methods: In COMET 3029 patients with CHF in NYHA II-IV and EF<40% were randomised to carvedilol (C) or metoprolol tartrate (M) and were followed for an average of 58 months. In 2596 patients with no baseline edema (85.7%), we analyzed the impact of BMI and weight change on survival and a combined endpoint of death or all-cause hospitalization.
Results: For each 1.0 unit increase in BMI, the risk of death decreased by 6.1% (p<0.0001), independently of treatment assignement. Event rates for 58 months of follow-up and hazard ratios (HR) in each BMI category are shown below:

BMI group	%death	HR	%death/hospitalization	HR
<22 (n=302)	48.9	2.29***	81.6	1.60 ***
22-<25 (n=672)	39.3	1.70***	75.6	1.24 **
25-<30 (n=1145)	32.1	1.28*	72.8	1.13 +
≥30 (n=474)	25.3	1.00	68.1	1.00

+ p=0.056, * p<0.05, ** p<0.003, *** p<0.0001

Excluding weight observations with edema, the respective weight change at 1 and 3 yrs follow-up were 1.6±5.0 and 2.2±6.2 kg on C and 1.6±4.8 and 2.0±6.2 kg on M (p>0.15 for all visits between 4 and 60 months). At 1 and 5 years, the cumulative incidence of ≥6% weight loss was 13 / 29% (C) and 11 / 26% (M, p>0.2). The respective incidence of ≥5% weight gain was 32 / 51% (C) and 33 / 52% (M, p>0.2). In time-dependent models considering the complete follow-up period, we found that both weight loss and weight gain carried prognostic value, independently of BMI and treatment assignment. Per percent weight loss, mortality was increased 8.7% (95%CI 7.1-10.3%, P<0.0001). Per percent weight gain, mortality was reduced 2.2% (0.6-3.7%, p=0.0058).
Conclusion: In CHF, lower BMI and weight loss are both associated with higher mortality and hospitalization rates. Weight gain is associated with lower mortality and lower hospitalization rates. Treatments promoting weight gain may be beneficial for patients with CHF.

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ACC/AHA PRACTICE GUIDELINES

ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult: Executive Summary

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure)

Developed in Collaboration with the International Society for Heart and Lung Transplantation

Endorsed by the Heart Failure Society of America

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The document was approved by the American College of Cardiology Board of Trustees in November 2001 and the American Heart Association Science Advisory and Coordinating Committee in September 2001.

When citing this document, the American College of Cardiology and the American Heart Association would appreciate the following citation format: Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, Francis GS, Ganiats TG, Goldstein S, Gregoratos G, Jessup ML, Noble RJ, Packer M, Silver MA, Stevenson LW. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol 2001;38:2101–13.

The American College of Cardiology and the American Heart Association make every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to provide disclosure statements of all such relationships that might be perceived as real or potential conflicts of interest. These statements are reviewed by the parent task force, reported orally to all members of the writing panel at the first meeting, and updated as changes occur.

This document, as well as the corresponding full-text guidelines, is available on the World Wide Web sites of the American College of Cardiology (www.acc.org) and the American Heart Association (www.americanheart.org). Single reprints of the executive summary are available for $5.00 each by calling 800-253-4636 (US only) or writing the American College of Cardiology, Educational Services, 9111 Old Georgetown Road, Bethesda, MD 20814-1699. To purchase additional reprints up to 999 copies, call 800-611-6083 (US only) or fax 413-665-2671; 1000 or more copies, call 214-706-1466, fax 214-691-6342, or e-mail pubauth@heart.org (specify version: Executive Summary—71-0125; Full Text—71-1026).

*Former Task Force member during this writing effort.

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I. INTRODUCTION

Heart failure (HF) is a major public health problem in the United States. Nearly 5 million patients in this country have HF, and nearly 500,000 patients are diagnosed with HF for the first time each year. The disorder is the underlying reason for 12 to 15 million office visits and 6.5 million hospital days each year (1). During the last 10 years, the annual number of hospitalizations has increased from approximately 550,000 to nearly 900,000 for HF as a primary diagnosis and from 1.7 to 2.6 million for HF as a primary or secondary diagnosis (2). Nearly 300,000 patients die of HF as a primary or contributory cause each year, and the number of deaths has increased steadily despite advances in treatment.

HF is primarily a disease of the elderly (3). Approximately 6% to 10% of people older than 65 years have HF (4), and approximately 80% of patients hospitalized with HF are more than 65 years old (2). HF is the most common Medicare diagnosis-related group, and more Medicare dollars are spent for the diagnosis and treatment of HF than for any other diagnosis (5). The total inpatient and outpatient costs for HF in 1991 were approximately $38.1 billion, which was approximately 5.4% of the healthcare budget that year (1). In the United States, approximately $500 million annually is spent on drugs for the treatment of HF.

The American College of Cardiology (ACC) and the American Heart Association (AHA) first published guidelines for the evaluation and management of HF in 1995 (6). Since that time, a great deal of progress has been made in the development of both pharmacological and nonpharmacological approaches to treatment for this common, costly, disabling, and generally fatal disorder. For this reason, the 2 organizations believed that the time was right to reassess and update these guidelines, fully recognizing that the optimal therapy of HF remains a work in progress and that future guidelines will supersede these.

The writing committee was composed of 7 members who represented the ACC and AHA, as well as invited participants from the American College of Chest Physicians, the Heart Failure Society of America, the International Society for Heart and Lung Transplantation, the American Academy of Family Physicians, and the American College of Physicians–American Society of Internal Medicine. Both the academic and private practice sectors were represented. This document was reviewed by 3 official reviewers nominated by the ACC, 3 official reviewers nominated by the AHA, 1 reviewer nominated by the Heart Failure Society of America, 1 reviewer nominated by the International Society for Heart and Lung Transplantation, 1 reviewer nominated by the American Academy of Family Physicians, 1 reviewer nominated by the National Heart Foundation of Australia, the ACC Hypertensive Disease Committee and 16 content reviewers.

In formulating the present document, the writing committee decided to take a new approach to the classification of HF that emphasized both the evolution and progression of the disease. In doing so, we identified 4 stages of HF. Stage A identifies the patient who is at high risk for developing HF but has no structural disorder of the heart, Stage B refers to a patient with a structural disorder of the heart but who has never developed symptoms of HF; Stage C denotes the patient with past or current symptoms of HF associated with underlying structural heart disease; and Stage D designates the patient with end-stage disease who requires specialized treatment strategies such as mechanical circulatory support, continuous inotropic infusions, cardiac transplantation, or hospice care (see Table 1 and Fig. 1). Only the latter 2 stages, of course, qualify for the traditional clinical diagnosis of HF for diagnostic or coding purposes. This classification recognizes that there are established risk factors and structural prerequisites for the development of HF and that therapeutic interventions performed even before the appearance of left ventricular dysfunction or symptoms can reduce the morbidity and mortality of HF. This classification system is intended to complement but not to replace the New York Heart Association (NYHA) functional classification, which primarily gauges the severity of symptoms in patients who are in stage C or D. It has been recognized for many years, however, that the NYHA functional classification reflects a subjective assessment by a physician and changes frequently over short periods of time and that the treatments used do not differ significantly across the classes. Therefore, the committee believed that a staging system was needed that would reliably and objectively identify patients in the course of their disease and would be linked to treatments that were uniquely appropriate at each stage of their illness. According to this new approach, patients would be expected to advance from one stage to the next unless progression of the disease was slowed or stopped by treatment. This new classification scheme adds a useful dimension to our thinking about HF similar to that achieved by staging systems for other disorders (e.g., those used in the classification of cancer).

Table 1. Stages of HF

Stage	Description	Examples
A	Patients at high risk of developing HF because of the presence of conditions that are strongly associated with the development of HF. Such patients have no identified structural or functional abnormalities of the pericardium, myocardium, or cardiac valves and have never shown signs or symptoms of HF.	Systemic hypertension; coronary artery disease; diabetes mellitus; history of cardiotoxic drug therapy or alcohol abuse; personal history of rheumatic fever; family history of cardiomyopathy.
B	Patients who have developed structural heart disease that is strongly associated with the development of HF but who have never shown signs or symptoms of HF.	Left ventricular hypertrophy or fibrosis; left ventricular dilatation or hypocontractility; asymptomatic valvular heart disease; previous myocardial infarction.
C	Patients who have current or prior symptoms of HF associated with underlying structural heart disease.	Dyspnea or fatigue due to left ventricular systolic dysfunction; asymptomatic patients who are undergoing treatment for prior symptoms of HF.
D	Patients with advanced structural heart disease and marked symptoms of HF at rest despite maximal medical therapy and who require specialized interventions.	Patients who are frequently hospitalized for HF or cannot be safely discharged from the hospital; patients in the hospital awaiting heart transplantation; patients at home receiving continuous intravenous support for symptom relief or being supported with a mechanical circulatory assist device; patients in a hospice setting for the management of HF.

HF indicates heart failure.

All recommendations provided in this document follow the format of previous ACC/AHA guidelines:

Class I: Conditions for which there is evidence and/or general agreement that a given procedure/therapy is useful and effective.

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of performing the procedure/therapy.

Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.

Class IIb: Usefulness/efficacy is less well established by evidence/opinion.

Class III: Conditions for which there is evidence and/or general agreement that a procedure/therapy is not useful/effective and in some cases may be harmful.

The recommendations listed in this document are evidence based whenever possible. Pertinent medical literature in the English language was identified through a series of computerized literature searches (including Medline and EMBASE) and a manual search of selected articles. References selected and published in this document are representative but not all-inclusive.

The levels of evidence on which these recommendations are based were ranked as level A if the data were derived from multiple randomized clinical trials, level B when data were derived from a single randomized trial or nonrandomized studies, and level C when the consensus opinion of experts was the primary source of recommendation. The strength of evidence does not necessarily reflect the strength of a recommendation. A treatment may be considered controversial although it has been evaluated in controlled clinical trials; conversely, a strong recommendation may be based on years of clinical experience and be supported only by historical data or by no data at all.

The committee elected to focus this document on the prevention of HF, as well as the evaluation and management of chronic HF in the adult patient with left ventricular systolic and diastolic dysfunction. It specifically did not consider acute HF, which might merit a separate set of guidelines and which is addressed in part in the ACC/AHA guidelines for the management of patients with acute myocardial infarction (7). We have also excluded HF in children, both because the underlying causes of HF in children differ from those in adults and because none of the controlled trials of treatments for HF have included children. We have not considered the management of HF due to primary valvular disease (see ACC/AHA guidelines on management of patients with valvular heart disease) (8) or congenital malformations, and we have not included recommendations for the treatment of specific myocardial disorders (e.g., hemochromatosis, sarcoidosis, or amyloidosis).

The ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult were approved for publication by the governing bodies of the ACC and AHA. These guidelines will be reviewed annually after publication and will be considered current unless the ACC/AHA Task Force on Practice Guidelines revises or withdraws them from circulation.

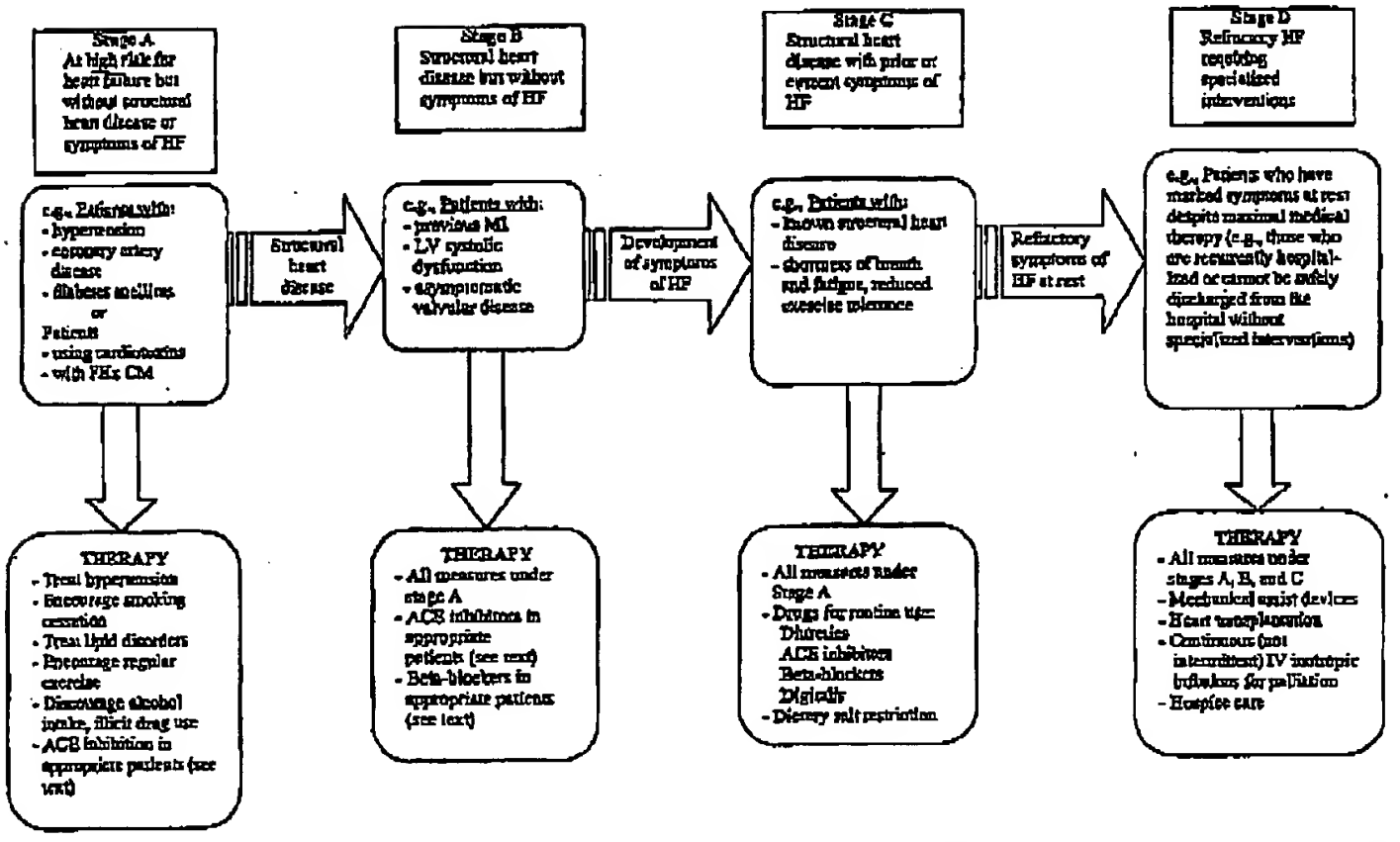

Figure 1. Stages in the evolution of HF and recommended therapy by stage. FHx CM indicates family history of cardiomyopathy; MI, myocardial infarction; LV, left ventricular; and IV, intravenous.

These practice guidelines are intended to assist physicians in clinical decision making by describing a range of generally acceptable approaches for the prevention, diagnosis, and management of HF. The guidelines attempt to define practices that meet the needs of most patients under most circumstances. However, the ultimate judgment regarding the care of a particular patient must be made by the physician in light of all of the circumstances that are relevant to that patient. The various therapeutic strategies described in this document can be viewed as a checklist to be considered for each patient in an attempt to individualize treatment for an evolving disease process. Every patient is unique, not only in terms of his or her cause and course of HF, but also in terms of his or her personal and cultural approach to the disease. Guidelines can only provide an outline for evidence-based decisions or recommendations for individual care; these guidelines are meant to provide that outline.

II. CHARACTERIZATION OF HF AS A CLINICAL SYNDROME

HF is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. The cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary and peripheral edema. Both abnormalities can impair the functional capacity and quality of life of affected individuals, but they may not necessarily dominate the clinical picture at the same time.

Coronary artery disease is the underlying cause of HF in approximately two thirds of patients with left ventricular systolic dysfunction (9). The remainder have nonischemic causes of systolic dysfunction and may have an identifiable cause (e.g., hypertension, valvular disease, myocardial toxins, or myocarditis) or may have no discernible cause (e.g., idiopathic dilated cardiomyopathy).

The classification system that is most commonly used to quantify the degree of functional limitation imposed by HF is one first developed by the NYHA (10). This system assigns patients to 1 of 4 functional classes depending on the degree of effort needed to elicit symptoms: patients may have symptoms of HF at rest (class IV), on less-than-ordinary exertion (class III), on ordinary exertion (class II), or only at levels that would limit normal individuals (class I). The mechanisms responsible for exercise intolerance in patients with chronic HF have not been clearly defined. Patients with a very low ejection fraction may be asymptomatic, whereas patients with preserved left ventricular systolic function may have severe disability. The apparent discordance between the severity of systolic dysfunction and the degree of functional impairment is not well understood despite intense investigation.

Left ventricular dysfunction begins with some injury to

the myocardium and is usually a progressive process, even in the absence of a new identifiable insult to the myocardium. The principal manifestation of such progression is a process known as remodeling, which occurs in association with homeostatic attempts to decrease wall stress through increases in wall thickness. This ultimately results in a change in the geometry of the left ventricle such that the chamber dilates, hypertrophies, and becomes more spherical. The process of cardiac remodeling generally precedes the development of symptoms, occasionally by months or even years. The process of remodeling continues after the appearance of symptoms and may contribute importantly to worsening of symptoms despite treatment.

The committee struggled with its perception that many clinicians do not appreciate the progressive nature of left ventricular dysfunction and HF or the importance of screening and prophylaxis for them, principles that are quite analogous to well-recognized strategies in the field of oncology. For this reason, it believed that the progression to and evolution of HF could appropriately be characterized by considering 4 stages in the evolution of the disease as described in the Introduction and Table 1. This classification scheme recognizes that HF, like coronary artery disease, has established risk factors; that the evolution of HF has asymptomatic and symptomatic phases; and that treatments prescribed at each stage can reduce the morbidity and mortality of HF.

III. ASSESSMENT OF PATIENTS

A. Initial Evaluation of Patients and Detection of Predisposing Conditions

1. Identification of Patients. In general, patients with left ventricular dysfunction present to the physician in 1 of 3 ways: with a syndrome of decreased exercise tolerance; with a syndrome of fluid retention; or with no symptoms and incidentally discovered left ventricular dysfunction.

2. Identification of Structural Abnormality. A complete history and physical examination are the first steps in evaluating the structural abnormality or cause responsible for the development of HF. Although the history and physical examination may provide important clues about the nature of the underlying cardiac abnormality, identification of the structural abnormality leading to HF generally requires either noninvasive or invasive imaging of the cardiac structures. The single most useful diagnostic test in the evaluation of patients with HF is the 2-dimensional echocardiogram, coupled with Doppler flow studies. Other tests may be used to provide information regarding the nature and severity of the cardiac abnormality. Radionuclide ventriculography can provide highly accurate measurements of global and regional function and assessment of ventricular enlargement, but it is unable to directly assess valvular abnormalities or cardiac hypertrophy. Both chest radiography and 12-lead electrocardiograms are considered to provide baseline information in most patients, but because they are both insensitive and nonspecific, neither the chest radiograph nor the electrocardiogram alone should form the primary basis for determining the specific cardiac abnormality responsible for the development of HF.

Recently, the measurement of circulating levels of brain natriuretic peptide has become available as a means of identifying patients with elevated left ventricular filling pressures who are likely to exhibit signs and symptoms of HF. The assessment of this peptide cannot reliably distinguish patients with systolic from those with diastolic dysfunction. However, it has been widely investigated as a biochemical marker of morbidity and mortality in patients with known HF (11) and as an aid in differentiating dyspnea due to HF from dyspnea due to other causes in an emergency setting (12). The role of brain natriuretic peptide measurement in the identification and management of patients with symptomatic or asymptomatic left ventricular dysfunction remains to be fully clarified.

3. Evaluation of the Cause of Ventricular Dysfunction. Identification of the disorder leading to HF may be important, because some causes of left ventricular dysfunction are reversible or treatable. However, it may not be possible to discern the cause of HF in many patients who present with this syndrome, and in others, the underlying condition may not be amenable to treatment. Hence, physicians should focus their efforts on diagnoses that have some potential for improvement with therapy directed at the underlying condition. Evaluation of potential causative factors should include taking a patient and family history, general laboratory testing, evaluation of the possibility of coronary artery disease, and evaluation of the possibility of primary myocardial disease.

B. Ongoing Evaluation of HF

Once the nature and cause of the structural abnormalities leading to the development of HF have been defined, physicians should focus on the clinical assessment of patients, both during the initial presentation and during subsequent visits. This ongoing review of the patient's clinical status is critical to the appropriate selection and monitoring of treatment. It should include assessment of functional capacity, assessment of volume status, laboratory evaluation, and assessment of prognosis.

Recommendations for the Evaluation of Patients With HF

Class I

1. **Thorough history and physical examination to identify cardiac and noncardiac disorders that might lead to the development of HF or accelerate the progression of HF. (*Level of Evidence: C*)**
2. **Initial and ongoing assessment of patient's ability to perform routine and desired activities of daily living. (*Level of Evidence: C*)**
3. **Initial and ongoing assessment of volume status. (*Level of Evidence: C*)**

4. Initial measurement of complete blood count, urinalysis, serum electrolytes (including calcium and magnesium), blood urea nitrogen, serum creatinine, blood glucose, liver function tests, and thyroid-stimulating hormone. (*Level of Evidence: C*)
5. Serial monitoring of serum electrolytes and renal function. (*Level of Evidence: C*)
6. Initial 12-lead electrocardiogram and chest radiograph. (*Level of Evidence: C*)
7. Initial 2-dimensional echocardiography with Doppler or radionuclide ventriculography to assess left ventricular systolic function. (*Level of Evidence: C*)
8. Cardiac catheterization with coronary arteriography in patients with angina who are candidates for revascularization. (*Level of Evidence: B*)

Class IIa

1. Cardiac catheterization with coronary arteriography in patients with chest pain who have not had evaluation of their coronary anatomy and who have no contraindications to coronary revascularization. (*Level of Evidence: C*)
2. Cardiac catheterization with coronary arteriography in patients with known or suspected coronary artery disease but without angina who are candidates for revascularization. (*Level of Evidence: C*)
3. Noninvasive imaging to detect ischemia and viability in patients with known coronary artery disease and no angina who are being considered for revascularization. (*Level of Evidence: C*)
4. Maximal exercise testing with measurement of respiratory gas exchange and/or blood oxygen saturation to help determine whether HF is the cause of exercise limitation when the contribution of HF is uncertain. (*Level of Evidence: C*)
5. Maximal exercise testing with measurement of respiratory gas exchange to identify high-risk patients who are candidates for cardiac transplantation or other advanced treatments. (*Level of Evidence: B*)
6. Echocardiography in asymptomatic first-degree relatives of patients with idiopathic dilated cardiomyopathy. (*Level of Evidence: C*)
7. Repeat measurement of ejection fraction in patients who have had a change in clinical status or who have experienced or recovered from a clinical event or received treatment that might have had a significant effect on cardiac function. (*Level of Evidence: C*)
8. Screening for hemochromatosis. (*Level of Evidence: C*)
9. Measurement of serum antinuclear antibody, rheumatoid factor, urinary vanillylmandelic acid, and metanephrines in selected patients. (*Level of Evidence: C*)

Class IIb

1. Noninvasive imaging to define the likelihood of coronary artery disease in patients with left ventricular dysfunction. (*Level of Evidence: C*)
2. Maximal exercise testing with measurement of respiratory gas exchange to facilitate prescription of an appropriate exercise program. (*Level of Evidence: C*)
3. Endomyocardial biopsy in patients in whom an inflammatory or infiltrative disorder of the heart is suspected. (*Level of Evidence: C*)
4. Assessment of human immunodeficiency virus status. (*Level of Evidence: C*)

Class III

1. Endomyocardial biopsy in the routine evaluation of patients with HF. (*Level of Evidence: C*)
2. Routine Holter monitoring or signal-averaged electrocardiography. (*Level of Evidence: C*)
3. Repeat coronary arteriography or noninvasive testing for ischemia in patients for whom coronary artery disease has previously been excluded as the cause of left ventricular dysfunction. (*Level of Evidence: C*)
4. Routine measurement of circulating levels of norepinephrine or endothelin. (*Level of Evidence: C*)

IV. THERAPY

A. Patients at High Risk of Developing Left Ventricular Dysfunction (Stage A)

Many conditions or behaviors that are associated with an increased risk of HF can be identified before patients show any evidence of structural heart disease. Because early modification of these factors can often reduce the risk of HF, working with patients with these risk factors provides the earliest opportunity to reduce the impact of HF on public and individual health.

Recommendations for Patients at High Risk of Developing HF (Stage A)

Class I

1. Control of systolic and diastolic hypertension in accordance with recommended guidelines. (*Level of Evidence: A*)
2. Treatment of lipid disorders in accordance with recommended guidelines. (*Level of Evidence: B*)
3. Avoidance of patient behaviors that may increase the risk of HF (e.g., smoking, alcohol consumption, and illicit drug use). (*Level of Evidence: C*)
4. Angiotensin converting enzyme (ACE) inhibition in patients with a history of atherosclerotic vascular disease, diabetes mellitus, or hypertension and associated cardiovascular risk factors. (*Level of Evidence: B*)
5. Control of ventricular rate in patients with supraventricular tachyarrhythmias. (*Level of Evidence: B*)
6. Treatment of thyroid disorders. (*Level of Evidence: C*)
7. Periodic evaluation for signs and symptoms of HF. (*Level of Evidence: C*)

Class IIa

Noninvasive evaluation of left ventricular function in patients with a strong family history of cardiomyopathy or in those receiving cardiotoxic interventions. (*Level of Evidence: C*)

Class III

1. Exercise to prevent the development of HF. (*Level of Evidence: C*)
2. Reduction of dietary salt beyond that which is prudent for healthy individuals in patients without hypertension or fluid retention. (*Level of Evidence: C*)
3. Routine testing to detect left ventricular dysfunction in patients without signs or symptoms of HF or evidence of structural heart disease. (*Level of Evidence: C*)
4. Routine use of nutritional supplements to prevent the development of structural heart disease. (*Level of Evidence: C*)

B. Patients With Left Ventricular Dysfunction Who Have Not Developed Symptoms (Stage B)

Patients without symptoms but who have had a myocardial infarction and patients without symptoms who have evidence of left ventricular dysfunction are at considerable risk of developing HF. The likelihood of developing clinical HF can be diminished by the use of therapies that reduce the risk of additional injury, the process of remodeling, and the progression of left ventricular dysfunction. However, as with patients with no structural heart disease, there is no evidence that control of dietary sodium, participation in regular exercise, or use of nutritional supplements can prevent the development of HF in patients with a recent or remote myocardial infarction with or without left ventricular systolic dysfunction.

Recommendations for Patients With Asymptomatic Left Ventricular Systolic Dysfunction (Stage B)

Class I

1. ACE inhibition in patients with a recent or remote history of myocardial infarction regardless of ejection fraction. (*Level of Evidence: A*)
2. ACE inhibition in patients with a reduced ejection fraction, whether or not they have experienced a myocardial infarction. (*Level of Evidence: B*)
3. Beta-blockade in patients with a recent myocardial infarction regardless of ejection fraction. (*Level of Evidence: A*)
4. Beta-blockade in patients with a reduced ejection fraction, whether or not they have experienced a myocardial infarction. (*Level of Evidence: B*)
5. Valve replacement or repair for patients with hemodynamically significant valvular stenosis or regurgitation. (*Level of Evidence: B*)
6. Regular evaluation for signs and symptoms of HF. (*Level of Evidence: C*)
7. Measures listed as class I recommendations for patients in stage A. (*Levels of Evidence: A, B, and C as appropriate*).

Class IIb

Long-term treatment with systemic vasodilators in patients with severe aortic regurgitation. (*Level of Evidence: B*)

Class III

1. Treatment with digoxin in patients with left ventricular dysfunction who are in sinus rhythm. (*Level of Evidence: C*)
2. Reduction of dietary salt beyond that which is prudent for healthy individuals in patients without hypertension or fluid retention. (*Level of Evidence: C*)
3. Exercise to prevent the development of HF. (*Level of Evidence: C*)
4. Routine use of nutritional supplements to treat structural heart disease or prevent the development of symptoms of HF. (*Level of Evidence: C*)

C. Patients With Left Ventricular Dysfunction With Current or Prior Symptoms (Stage C)

1. General Measures. Measures listed as class I recommendations for patients in stages A and B are also appropriate for patients with current or prior symptoms of HF (see Section V). In addition, moderate sodium restriction is indicated, along with daily measurement of weight, to permit effective use of lower and safer doses of diuretic drugs. Immunization with influenza and pneumococcal vaccines may reduce the risk of a respiratory infection. Although most patients should not participate in heavy labor or exhaustive sports, physical activity should be encouraged, except during periods of acute decompensation or in patients with suspected myocarditis, because restriction of activity promotes physical deconditioning, which may adversely affect clinical status and contribute to the exercise intolerance of patients with HF (13–16).

Of the general measures that should be pursued in patients with HF, possibly the most effective yet least utilized is close attention and follow-up. Noncompliance with diet and medications can rapidly and profoundly affect the clinical status of patients, and increases in body weight and minor changes in symptoms commonly precede the major clinical episodes that require emergency care or hospitalization. Patient education and close supervision, which includes surveillance by the patient and his or her family between physician visits, can reduce the likelihood of noncompliance and can often lead to the detection of changes in body weight or clinical status early enough to allow the patient or a healthcare provider an opportunity to institute treatments that can prevent clinical deterioration and hospitalization. Supervision between physician visits ideally may be performed by a nurse or physician assistant

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with special training in the care of patients with HF. Such an approach has been reported to have significant clinical benefits (17–20).

2. Drugs Recommended for Routine Use. Most patients with symptomatic left ventricular dysfunction should be routinely managed with a combination of 4 types of drugs: a diuretic, an ACE inhibitor, a beta-adrenergic blocker, and (usually) digitalis (21). The value of these drugs has been established in numerous large-scale clinical trials, and the evidence supporting a central role for their use is compelling and persuasive. Patients with evidence of fluid retention should be given a diuretic until a euvolemic state is achieved, and diuretic therapy should be continued to prevent the recurrence of fluid retention. Even if the patient has responded favorably to the diuretic, treatment with an ACE inhibitor and a beta-blocker should be initiated and maintained in patients who can tolerate them, because they have been shown to favorably influence the long-term prognosis of HF. Therapy with digoxin may be initiated at any time to reduce symptoms and enhance exercise tolerance.

3. Interventions to Be Considered for Use in Selected Patients. Several interventions have been shown in controlled clinical trials to be useful in a limited cohort of patients with HF. Some of these are undergoing active investigation in large-scale trials to determine whether their role in the management of HF might justifiably be expanded. They include aldosterone antagonists, angiotensin receptor blockers, hydralazine and isosorbide dinitrate, and exercise training.

4. Drugs and Interventions Under Active Investigation. Several drugs and interventions are under active evaluation in long-term large-scale trials because they showed promise in pilot studies that involved small numbers of patients. Until the results of definitive trials are available, none of these interventions can be recommended for use in patients with HF. These include vasopeptidase inhibitors, cytokine antagonists, endothelin antagonists, synchronized biventricular pacing, external counterpulsation, and techniques for respiratory support.

5. Interventions of Unproved Value and Not Recommended. Interventions of unproved value that are not recommended include nutritional supplements and hormonal therapies, intermittent intravenous positive inotropic therapy, and dynamic cardiomyoplasty.

Recommendations for Treatment of Symptomatic Left Ventricular Systolic Dysfunction (Stage C)

Class I

1. Diuretics in patients who have evidence of fluid retention. (*Level of Evidence: A*)
2. ACE inhibition in all patients unless contraindicated. (*Level of Evidence: A*)
3. Beta-adrenergic blockade in all stable patients unless contraindicated. Patients should have no or minimal evidence of fluid retention and should not have required treatment recently with an intravenous positive inotropic agent. (*Level of Evidence: A*)
4. Digitalis for the treatment of symptoms of HF, unless contraindicated. (*Level of Evidence: A*)
5. Withdrawal of drugs known to adversely affect the clinical status of patients (e.g., nonsteroidal anti-inflammatory drugs, most antiarrhythmic drugs, and most calcium channel blocking drugs). (*Level of Evidence: B*)
6. Measures listed as class I recommendations for patients in stages A and B (*Levels of Evidence: A, B, and C as appropriate*).

Class IIa

1. Spironolactone in patients with recent or current class IV symptoms, preserved renal function, and a normal potassium concentration. (*Level of Evidence: B*)
2. Exercise training as an adjunctive approach to improve clinical status in ambulatory patients. (*Level of Evidence: A*)
3. Angiotensin receptor blockade in patients who are being treated with digitalis, diuretics, and a beta-blocker and who cannot be given an ACE inhibitor because of cough or angioedema. (*Level of Evidence: A*)
4. A combination of hydralazine and a nitrate in patients who are being treated with digitalis, diuretics, and a beta-blocker and who cannot be given an ACE inhibitor because of hypotension or renal insufficiency. (*Level of Evidence: B*)

Class IIb

1. Addition of an angiotensin receptor blocker to an ACE inhibitor. (*Level of Evidence: B*)
2. Addition of a nitrate, alone or in combination with hydralazine, to an ACE inhibitor in patients who are also being given digitalis, diuretics, and a beta-blocker. (*Level of Evidence: B*)

Class III

1. Long-term intermittent use of an infusion of a positive inotropic drug. (*Level of Evidence: C*)
2. Use of an angiotensin receptor blocker instead of an ACE inhibitor in patients with HF who have not been given or who can tolerate an ACE inhibitor. (*Level of Evidence: B*)
3. Use of an angiotensin receptor blocker before a beta-blocker in patients with HF who are taking an ACE inhibitor. (*Level of Evidence: A*)
4. Use of a calcium channel blocking drug as a treatment for HF. (*Level of Evidence: B*)
5. Routine use of nutritional supplements (coenzyme Q10, carnitine, taurine, and antioxidants) or hormonal therapies (growth hormone or thyroid hormone) for the treatment of HF. (*Level of Evidence: C*)

D. Patients With Refractory End-Stage HF (Stage D)

Most patients with HF due to left ventricular systolic dysfunction respond favorably to pharmacological and non-

pharmacological treatments and enjoy a good quality of life and enhanced survival. However, despite optimal medical therapy, some patients do not improve with treatment or experience rapid recurrence of symptoms. Such patients generally have symptoms (including profound fatigue) at rest or on minimal exertion, cannot perform most activities of daily living, frequently have evidence of cardiac cachexia, and typically require repeated or prolonged hospitalizations for intensive management. These individuals represent the most advanced state of HF and should be considered for specialized treatment strategies such as mechanical circulatory support, continuous intravenous positive inotropic therapy, referral for cardiac transplantation, or hospice care. Before a patient is considered to have refractory HF, it is critical that physicians confirm the accuracy of the diagnosis; identify and reverse, if possible, any contributing conditions; and ensure that all conventional medical strategies have been optimally employed.

Many patients with advanced HF have symptoms that are related to the retention of salt and water and thus will respond favorably to interventions designed to restore sodium balance. Hence, a critical step in the successful management of end-stage HF is the recognition and meticulous control of fluid retention.

Controlled trials suggest that patients with advanced HF respond favorably to treatment with both ACE inhibitors and beta-blockers in a manner similar to those with mild to moderate disease (22,23). However, because neurohormonal mechanisms play an important role in the support of circulatory homeostasis as HF progresses, neurohormonal antagonism may be less well tolerated by patients with severe symptoms than by patients with mild symptoms. Patients who are at the end stage of their disease are at particular risk of developing hypotension and renal insufficiency after the administration of an ACE inhibitor and of experiencing worsening HF after treatment with a beta-blocker. As a result, patients with refractory HF may tolerate only small doses of these neurohormonal antagonists or may not tolerate them at all.

Many commonly performed cardiac surgical procedures (e.g., coronary artery bypass grafting and valve repair/replacement) are being performed with increasing frequency in patients with HF, including those with advanced symptoms. Revascularization is routinely recommended for patients with left ventricular dysfunction who have angina, but its role in patients without symptoms of ischemia remains controversial.

Cardiac transplantation is currently the only established surgical approach to the treatment of refractory HF, but it is available to no more than 2500 patients yearly in the United States (24). Alternative surgical and mechanical approaches for the treatment of end-stage HF are under development. Extracorporeal devices are approved for circulatory support in patients who are expected to recover from a major cardiac insult (e.g., postcardiotomy shock) or who are expected to receive a definitive treatment for HF (e.g., heart transplantation). Left ventricular assist devices provide similar degrees of hemodynamic support, but many are implantable and thus allow for patient ambulation and hospital discharge (25,26). One ongoing trial is evaluating the long-term utility of such a device in patients with refractory HF who are not candidates for a heart transplant.

Recommendations for Patients With Refractory End-Stage HF (Stage D)

Class I

1. Meticulous identification and control of fluid retention. (*Level of Evidence: B*)
2. Referral for cardiac transplantation in eligible patients. (*Level of Evidence: B*)
3. Referral to an HF program with expertise in the management of refractory HF. (*Level of Evidence: A*)
4. Measures listed as class I recommendations for patients in stages A, B, and C. (*Levels of Evidence: A, B, and C as appropriate*).

Class IIb

1. Pulmonary artery catheter placement to guide therapy in patients with persistently severe symptoms. (*Level of Evidence: C*)
2. Mitral valve repair or replacement for severe secondary mitral regurgitation. (*Level of Evidence: C*)
3. Continuous intravenous infusion of a positive inotropic agent for palliation of symptoms. (*Level of Evidence: C*)

Class III

1. Partial left ventriculectomy. (*Level of Evidence: C*)
2. Routine intermittent infusions of positive inotropic agents. (*Level of Evidence: B*)

V. TREATMENT OF SPECIAL POPULATIONS AND CONCOMITANT DISORDERS

Many patients with HF are members of subpopulations or have comorbid conditions that either contribute to the development of their HF or make the management of their HF symptoms more difficult. These factors need to be considered in the management of such patients.

1. Special Subpopulations. Many subgroups are underrepresented in most trials, and some present unique problems in HF management. These include women and men, racial minorities, and elderly patients.

2. Concomitant Disorders. Patients with left ventricular dysfunction frequently have associated cardiovascular and noncardiovascular disorders, the course or treatment of which may exacerbate the syndrome of HF. In many patients, appropriate management of these concomitant illnesses may produce clinical and prognostic benefits that may be as important as the treatment of HF itself. These concomitant conditions include cardiovascular disorders such as hypertension, hyperlipidemia, and diabetes mellitus; coronary artery disease; supraventricular arrhythmias; ven-

tricular arrhythmias and prevention of sudden death; and prevention of thrombotic events. Associated noncardiovascular disorders include renal insufficiency, pulmonary disease, cancer, and thyroid disease.

Recommendations for Management of Concomitant Diseases in Patients With HF

Class I

1. Control of systolic and diastolic hypertension in patients with HF in accordance with recommended guidelines. (*Level of Evidence: A*)
2. Nitrates and beta-blockers (in conjunction with diuretics) for the treatment of angina in patients with HF. (*Level of Evidence: B*)
3. Coronary revascularization in patients who have both HF and angina. (*Level of Evidence: A*)
4. Anticoagulants in patients with HF who have paroxysmal or chronic atrial fibrillation or a previous thromboembolic event. (*Level of Evidence: A*)
5. Control of the ventricular response in patients with HF and atrial fibrillation with a beta-blocker (or amiodarone, if the beta-blocker is contraindicated or not tolerated). (*Level of Evidence: A*)
6. Beta-adrenergic blockade (unless contraindicated) in patients with HF to reduce the risk of sudden death. Patients should have no or minimal fluid retention and should not have recently required treatment with an intravenous positive inotropic agent. (*Level of Evidence: A*)
7. Implantable cardioverter-defibrillator, alone or in combination with amiodarone, in patients with HF who have a history of sudden death, ventricular fibrillation, or hemodynamically destabilizing ventricular tachycardia. (*Level of Evidence: A*)

Class IIa

1. Antiplatelet agents for prevention of myocardial infarction and death in patients with HF who have underlying coronary artery disease. (*Level of Evidence: B*)
2. Digitalis to control the ventricular response in patients with HF and atrial fibrillation. (*Level of Evidence: A*)

Class IIb

1. Coronary revascularization in patients who have HF and coronary artery disease but no angina. (*Level of Evidence: B*)
2. Restoration of sinus rhythm by electrical cardioversion in patients with HF and atrial fibrillation. (*Level of Evidence: C*)
3. Amiodarone to prevent sudden death in patients with HF and asymptomatic ventricular arrhythmias. (*Level of Evidence: B*)
4. Anticoagulation in patients with HF who do not have atrial fibrillation or a previous thromboembolic event. (*Level of Evidence: B or C*)

Class III

1. Routine use of an implantable cardioverter-defibrillator in patients with HF. (*Level of Evidence: C*)
2. Class I or III antiarrhythmic drugs (except amiodarone) in patients with HF for the prevention or treatment of asymptomatic ventricular arrhythmias. (*Level of Evidence: A*)
3. Ambulatory electrocardiographic monitoring for the detection of asymptomatic ventricular arrhythmias. (*Level of Evidence: A*)

VI. DIASTOLIC DYSFUNCTION

Approximately 20% to 40% of patients with HF have preserved left ventricular systolic function and (in the absence of valvular disease) are believed to have an impairment of ventricular relaxation as the primary mechanism leading to symptoms (27–31). Several recognized myocardial disorders are associated with diastolic dysfunction, including restrictive cardiomyopathy, obstructive and nonobstructive hypertrophic cardiomyopathy, and infiltrative cardiomyopathies. However, the vast majority of patients who present with HF and normal systolic function do not have a defined myocardial disease but nevertheless have a clinically significant impairment of diastolic function.

Many of the changes that occur in the cardiovascular system as a result of aging have a greater impact on diastolic function than on systolic performance (32). HF associated with preserved systolic function is primarily a disease of elderly women, most of whom have hypertension (28). These patients suffer considerably from dyspnea and fatigue, which can limit their exercise tolerance and quality of life, and they are hospitalized frequently for clinical stabilization (33). Although the risk of death in these patients appears to be lower than in patients with HF and poor systolic function, the management of these patients still has major socioeconomic implications (34).

It is difficult to be precise about the diagnosis of diastolic dysfunction. Noninvasive methods, especially those that rely on Doppler echocardiography, have been developed to assist in such diagnosis. In practice, however, the diagnosis of diastolic HF is generally based on the finding of typical symptoms and signs of HF in a patient who is shown to have a normal left ventricular ejection fraction and no valvular abnormalities on echocardiography.

In contrast to the treatment of HF due to systolic dysfunction, few clinical trials are available to guide the management of patients with HF due to diastolic dysfunction. Although controlled studies have been performed with digitalis, ACE inhibitors, angiotensin receptor antagonists, beta-blockers, and calcium channel blockers in patients with HF who had a normal left ventricular ejection fraction, these trials have been small or have produced inconclusive results (35–39). Nevertheless, many patients with diastolic HF receive treatment with these drugs because of the presence of comorbid conditions (i.e., atrial fibrillation,

hypertension, diabetes, or coronary artery disease). In addition, recommendations regarding the use of anticoagulation and antiarrhythmic agents apply to both systolic and diastolic HF.

In the absence of controlled clinical trials, the management of patients with diastolic dysfunction is frequently determined by a set of therapeutic principles (31). These include control of blood pressure, control of tachycardia, reduction in central blood volume, and alleviation of myocardial ischemia.

Recommendations for Management of HF and Preserved Systolic Function

Class I

1. Control of systolic and diastolic hypertension in accordance with published guidelines. (*Level of Evidence: A*)
2. Control of ventricular rate in patients with atrial fibrillation. (*Level of Evidence: C*)
3. Diuretics to control pulmonary congestion and peripheral edema. (*Level of Evidence: C*)

Class IIa

Coronary revascularization in patients with coronary artery disease in whom symptomatic or demonstrable myocardial ischemia is judged to have an adverse effect on diastolic function. (*Level of Evidence: C*)

Class IIb

1. Restoration of sinus rhythm in patients with atrial fibrillation. (*Level of Evidence: C*)
2. Use of beta-adrenergic blocking agents, ACE inhibitors, angiotensin receptor blockers, or calcium antagonists in patients with controlled hypertension to minimize symptoms of HF. (*Level of Evidence: C*)
3. Digitalis to minimize symptoms of HF. (*Level of Evidence: C*)

VII. END-OF-LIFE CONSIDERATIONS

Although issues surrounding end-of-life care deserve attention for all chronic terminal diseases, several general principles merit particular discussion in the context of chronic HF (40,41). Education of both patient and family regarding the expected or anticipated course of illness, final treatment options, and planning should be undertaken before the patient becomes too ill to participate in decisions. Discussions regarding treatment preferences, living wills, and advance directives should encompass a variety of likely contingencies that include responses to a potentially reversible exacerbation of HF, a cardiac arrest, a sudden catastrophic event such as a severe cerebrovascular accident, and worsening of major coexisting noncardiac conditions. In reviewing these issues with families, short-term intervention in anticipation of rapid recovery should be distinguished from prolonged life support without reasonable expectation of return to good functional capacity.

Hospice services have only recently been extended to patients dying of HF. Originally developed for patients with end-stage cancer, the focus of hospice care has now been expanded to the relief of symptoms other than pain (42). This is appropriate, because the suffering of patients with HF is characteristically linked to symptoms of breathlessness, and thus, compassionate care may require the frequent administration of intravenous diuretics and (in some cases) the continuous infusion of positive inotropic agents rather than the use of potent analgesics. Physicians caring for these patients, however, are becoming more comfortable with the prescription of anxiolytics and narcotics to ease distress during the last days.

Recommendations for End-of-Life Care

Class I

1. Ongoing patient and family education regarding prognosis for function and survival. (*Level of Evidence: C*)
2. Patient and family education about options for formulating and implementing advance directives. (*Level of Evidence: C*)
3. Continuity of medical care between inpatient and outpatient settings. (*Level of Evidence: C*)
4. Components of hospice care that are appropriate to the relief of suffering. (*Level of Evidence: C*)

Class III

Implantation of a cardioverter-defibrillator in patients with class IV symptoms who are not anticipated to experience clinical improvement from available treatments. (*Level of Evidence: C*)

VIII. IMPLEMENTATION OF PRACTICE GUIDELINES

Despite the publication of evidence-based guidelines (6,21,43), the current care of patients with HF remains suboptimal. Numerous studies document underutilization of key processes of care, such as use of ACE inhibitors in patients with decreased systolic function and the measurement of left ventricular ejection fraction (44–46). The relatively sparse literature on implementing practice guidelines for patients with HF can be divided into 2 areas: isolated provider interventions and disease-management systems approaches. It is clear that dissemination of a practice guideline must be accompanied by more intensive educational and behavioral change efforts to maximize the chances of improving physician practice patterns. The disease-management approach views HF as a chronic illness spanning the home, outpatient, and inpatient settings and involves multidisciplinary team care. Observational and randomized controlled trials have generally shown that disease-management programs reduce hospitalizations and can improve quality of life and functional status (20,47).

Insufficient evidence exists to make uniform recommen-

dations about the most appropriate roles for generalist physicians and cardiologists in the care of patients with HF. Many questions remain. Do generalist physicians and cardiologists provide similar levels of care for the noncardiac comorbid conditions frequently present in patients with HF? What is the optimal time for referral to a specialist? What is the most effective system of comanagement of patients by generalists and cardiologists? What is the most cost-effective entry point into a disease-management program? Regardless of the ultimate answers to these questions, all physicians and other healthcare providers must advocate and follow care practices that have been shown to improve patient outcomes. If a physician is not comfortable following a specific recommendation (e.g., the use of beta-blockers), then the physician should refer the patient to someone with expertise in HF. A collaborative model in which generalist and specialist physicians work together to optimize the care of patients with HF is likely to be most fruitful.

Recommendations for Implementing Practice Guidelines

Class I

1. Multifactorial interventions that attack different barriers to behavioral change. (*Level of Evidence: A*)
2. Multidisciplinary disease-management programs for patients at high risk for hospital admission or clinical deterioration. (*Level of Evidence: B*)
3. Academic detailing or educational outreach visits. (*Level of Evidence: A*)

Class IIa

1. Chart audit and feedback of results. (*Level of Evidence: A*)
2. Reminder systems. (*Level of Evidence: A*)
3. Local opinion leaders. (*Level of Evidence: A*)

Class IIb

Multidisciplinary disease-management programs for patients at low risk for hospital admission or clinical deterioration. (*Level of Evidence: B*)

Class III

1. Dissemination of guidelines without more intensive behavioral change efforts. (*Level of Evidence: A*)
2. Basic provider education alone. (*Level of Evidence: A*)

REFERENCES

1. O'Connell JB, Bristow M. Economic impact of heart failure in the United States: time for a different approach. J Heart Lung Transplant 1993;13:S107–12.
2. Haldeman GA, Croft JB, Giles WH, Rashidee A. Hospitalization of patients with heart failure: National Hospital Discharge Survey, 1985 to 1995. Am Heart J 1999;137:352–60.
3. Kannel WB, Belanger AJ. Epidemiology of heart failure. Am Heart J 1991;121:951–7.
4. Kannel WB. Epidemiology and prevention of cardiac failure: Framingham Study insights. Eur Heart J 1987;8 Suppl F:23–6.
5. Massie BM, Shah NB. Evolving trends in the epidemiologic factors of heart failure: rationale for preventive strategies and comprehensive disease management. Am Heart J 1997;133:703–12.
6. Williams JF, Jr., Bristow MR, Fowler MB, et al. ACC/AHA guidelines for the evaluation and management of heart failure: report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Evaluation and Management of Heart Failure). J Am Coll Cardiol 1995;26:1376–98.
7. Ryan TJ, Antman EM, Brooks NH, et al. 1999 update: ACC/AHA guidelines for the management of patients with acute myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). J Am Coll Cardiol 1999;34:890–911.
8. Bonow RO, Carabello B, de Leon AC, Jr., et al. Guidelines for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). Circulation 1998; 98:1949–84.
9. Gheorghiade M, Bonow RO. Chronic heart failure in the United States: a manifestation of coronary artery disease. Circulation 1998; 97:282–9.
10. The Criteria Committee of the New York Heart Association. Diseases of the Heart and Blood Vessels: Nomenclature and Criteria for Diagnosis. 6th ed. Boston, MA: Little Brown, 1964.
11. Tsutamoto T, Wada A, Maeda K, et al. Plasma brain natriuretic peptide level as a biochemical marker of morbidity and mortality in patients with asymptomatic or minimally symptomatic left ventricular dysfunction: comparison with plasma angiotensin II and endothelin-1. Eur Heart J 1999;20:1799–807.
12. Dao Q, Krishnaswamy P, Kazanegra R, et al. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. J Am Coll Cardiol 2001;37:379–85.
13. Chati Z, Zannad F, Jeandel C, et al. Physical deconditioning may be a mechanism for the skeletal muscle energy phosphate metabolism abnormalities in chronic heart failure. Am Heart J 1996;131:560–6.
14. Sinoway LI. Effect of conditioning and deconditioning stimuli on metabolically determined blood flow in humans and implications for congestive heart failure. Am J Cardiol 1988;62:45E–8E.
15. McKelvie RS, Teo KK, McCartney N, Humen D, Montague T, Yusuf S. Effects of exercise training in patients with congestive heart failure: a critical review. J Am Coll Cardiol 1995;25:789–96.
16. Mancini DM, Walter G, Reichek N, et al. Contribution of skeletal muscle atrophy to exercise intolerance and altered muscle metabolism in heart failure. Circulation 1992;85:1364–73.
17. Rich MW, Beckham V, Wittenberg C, Leven CL, Freedland KE, Carney RM. A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. N Engl J Med 1995;333:1190–5.
18. Shah NB, Der E, Ruggerio C, Heidenreich PA, Massie BM. Prevention of hospitalizations for heart failure with an interactive home monitoring program. Am Heart J 1998;135:373–8.
19. Fonarow GC, Stevenson LW, Walden JA, et al. Impact of a comprehensive heart failure management program on hospital readmission and functional status of patients with advanced heart failure. J Am Coll Cardiol 1997;30:725–32.
20. Philbin EF. Comprehensive multidisciplinary programs for the management of patients with congestive heart failure. J Gen Intern Med 1999;14:130–5.
21. Packer M, Cohn JN, Abraham WT, et al. Consensus recommendations for the management of chronic heart failure. Am J Cardiol 1999;83:1A–38A.
22. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316:1429–35.
23. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651–8.
24. Hosenpud JD, Bennett LE, Keck BM, Boucek MM, Novick RJ. The Registry of the International Society for Heart and Lung Transplantation: seventeenth official report: 2000. J Heart Lung Transplant 2000;19:909–31.
25. Goldstein DJ, Oz MC, Rose EA. Implantable left ventricular assist devices. N Engl J Med 1998;339:1522–33.

26. Ross EA, Moskowitz AJ, Packer M, et al. The REMATCH trial: rationale, design, and end points: Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure. Ann Thorac Surg 1999;67:723–30.
27. Aronow WS, Ahn C, Kronzon I. Prognosis of congestive heart failure in elderly patients with normal versus abnormal left ventricular systolic function associated with coronary artery disease. Am J Cardiol 1990; 66:1257–9.
28. Davis AP, Francis CM, Caruana L, Sutherland GR, McMurray JJ. The prevalence of left ventricular diastolic filling abnormalities in patients with suspected heart failure. Eur Heart J 1997;18:981–4.
29. Dougherty AH, Naccarelli GV, Gray EL, Hicks CH, Goldstein RA. Congestive heart failure with normal systolic function. Am J Cardiol 1984;54:778–82.
30. Iriarte M, Murga N, Sagastagoitia D, et al. Congestive heart failure from left ventricular diastolic dysfunction in systemic hypertension. Am J Cardiol 1993;71:308–12.
31. Litwin SE, Grossman W. Diastolic dysfunction as a cause of heart failure. J Am Coll Cardiol 1993;22:49A–55A.
32. Brutsaert DL, Sys SU, Gillebert TC. Diastolic failure: pathophysiology and therapeutic implications [published erratum appears in J Am Coll Cardiol 1993;22:1272]. J Am Coll Cardiol 1993;22:318–25.
33. Vasan RS, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. J Am Coll Cardiol 1995;26:1565–74.
34. Kessler KM. Heart failure with normal systolic function: update of prevalence, differential diagnosis, prognosis, and therapy. Arch Intern Med 1988;148:2109–11.
35. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997;336: 525–33.
36. Aronow WS, Kronzon I. Effect of enalapril on congestive heart failure treated with diuretics in elderly patients with prior myocardial infarction and normal left ventricular ejection fraction. Am J Cardiol 1993;71:602–4.
37. Aronow WS, Ahn C, Kronzon I. Effect of propranolol versus no propranolol on total mortality plus nonfatal myocardial infarction in older patients with prior myocardial infarction, congestive heart failure, and left ventricular ejection fraction > or = 40% treated with diuretics plus angiotensin-converting enzyme inhibitors. Am J Cardiol 1997;80:207–9.
38. Scraro JF, Zaret BL, Schulman DS, Black HR, Soufer R. Usefulness of verapamil for congestive heart failure associated with abnormal left ventricular diastolic filling and normal left ventricular systolic performance. Am J Cardiol 1990;66:981–6.
39. Warner JG, Jr, Metzger DC, Kitzman DW, Wesley DJ, Little WC. Losartan improves exercise tolerance in patients with diastolic dysfunction and a hypertensive response to exercise. J Am Coll Cardiol 1999;33:1567–72.
40. Doyle E, Hanks WC, MacDonald N. Oxford Textbook of Palliative Medicine. 2nd ed. Oxford, UK: Oxford Medical, 1998.
41. Lynn J, Harrold J. Handbook for Mortals: Guidance for People Facing Serious Illness. New York, NY: Oxford University Press, 1999.
42. AGS Ethics Committee. The care of dying patients: a position statement from the American Geriatrics Society. J Am Geriatr Soc 1995;43:577–8.
43. Konstam M, Dracup K, Baker D, et al. Heart Failure: Evaluation and Care of Patients With Left-Ventricular Systolic Dysfunction. Rockville, MD: Agency for Health Care Policy and Research; 1994. Clinical Practice Guideline, No. 11, AHCPR publication No. 94-1612.
44. Philbin EF, Rocco TA, Jr., Lindenmuth NW, Ulrich K, Jenkins PL. Clinical outcomes in heart failure: report from a community hospital-based registry. Am J Med 1999;107:549–55.
45. Stafford RS, Saglam D, Blumenthal D. National patterns of angiotensin-converting enzyme inhibitor use in congestive heart failure. Arch Intern Med 1997;157:2460–4.
46. Krumholz HM, Wang Y, Parent EM, Mockalis J, Perrillo M, Radford MJ. Quality of care for elderly patients hospitalized with heart failure. Arch Intern Med 1997;157:2242–7.
47. Rich MW. Heart failure disease management: a critical review. J Card Fail 1999;5:64–75.

The cardiac component of cardiac cachexia

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Background Recent evidence suggests the importance of noncardiac mechanisms in the genesis of the syndrome of cardiac cachexia. This raises the question of the relative role of the heart itself in this syndrome. This study sought to assess the cardiac dimensions, mass, and function and changes in these parameters over time in patients with chronic heart failure with and without cachexia.

Methods Doppler echocardiography was performed in 28 patients with nonedematous weight loss (>7.5% over a period of >6 months) compared with 56 matched patients without weight loss in a ratio of 1:2 (age 71 ± 13 vs 67 ± 8 years, $P = .07$; New York Heart Association class 2.9 ± 0.7 vs 2.6 ± 0.6, $P = .08$). In 18 cachectic and 35 noncachectic patients with previous echocardiographic recordings, we analyzed the changes in left ventricular (LV) dimensions and mass over time.

Results Cardiac dimensions including LV diastolic (69 ± 9 mm vs 67 ± 13 mm) and systolic cavity diameter (58 ± 11 mm vs 55 ± 15 mm), LV mass (480 ± 180 g vs 495 ± 190 g), and LV systolic and diastolic function including fractional shortening (16% ± 10% vs 18% ± 10%), isovolumic relaxation time (29 ± 22 ms vs 36 ± 27 ms), and E/A ratio (2.7 ± 1.6 vs 3.3 ± 2.9) did not differ between cachectic and noncachectic patients (all $P > .1$). By analyzing changes in LV mass over time, we found an increase (>20%) in 2 (11%) cachectic and 14 (40%) noncachectic patients and a decrease in LV mass (>20%) in 9 (50%) cachectic and 8 (23%) noncachectic patients (χ^2 test, $P < .05$).

Conclusions Although no specific cardiac abnormality could be detected echocardiographically in cachectic patients compared with patients with noncachectic chronic heart failure in a cross-sectional study, over time a significant loss of LV mass (>20%) occurs more frequently in patients with cardiac cachexia. (Am Heart J 2002;144:45-50.)

Long-standing severe chronic heart failure (CHF) is often accompanied by a loss of total body fat and lean body mass, known in its most severe form as cardiac cachexia. It has been recognized since the classic description by Hippocrates[1] and is associated with a particularly adverse prognosis.[2] A clear understanding of the mechanisms of reduced weight and wasting occurring in this syndrome still eludes us. A reduced blood flow to the limbs[3,4] may deprive tissues of the necessary substrates for normal protein turnover and growth.[5] The concept of generalized cellular hypoxia as a consequence of the failing heart is thought by some to be of central importance to the pathogenesis of cardiac cachexia.[6] However, growing evidence suggest the importance of noncardiac mechanisms in the genesis of the syndrome. These include malnutrition,[7,8] neurohormonal and immune activation with catabolic-anabolic imbalance,[9] cytokine activation,[10-13] and altered protein, fat, and bone mineral metabolism.[14-16] The increasing evidence of the "peripheral" component of cachexia raises the question of the relative importance of the "central," or cardiac component.

Although the cachectic heart has been described as a pathologic decrease in the size and mass of the heart,[17] no studies have followed changes in cardiac dimensions or mass over time in patients with CHF with cardiac cachexia. The purpose of this investigation was to assess cardiac dimensions, mass, and function and changes in these parameters over time in patients with CHF with and without cachexia by use of quantitative Doppler echocardiographic techniques.

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Methods

Patient population and characteristics

The target population for this study was all cachectic patients with CHF of ischemic or dilated cardiomyopathy ori-

gin, referred for an echocardiographic examination as part of their routine assessment at the Royal Brompton Hospital between 1992 and 1999. A total of 28 male consecutive patients with cardiac cachexia were studied. Cardiac cachexia was defined as documented nonedematous and nonintentional weight loss of >7.5% over a period of >6 months.[2] The diagnosis of heart failure was based on history, examination, electrocardiogram, chest radiography, and echocardiographic findings and made if both of the following were present: symptoms compatible with a diagnosis of heart failure, mainly exertional breathlessness for at least 6 months, and evidence of substantial impairment of left ventricular (LV) systolic function or LV filling on Doppler echocardiography. These patients were matched with 56 patients with CHF without weight loss in a ratio of 1:2. There was no difference between the 2 groups with and without cachexia with respect to the underlying cause of heart failure. Heart failure was of ischemic origin in 18 (64%) cachectic patients and in 37 (66%) noncachectic patients. The presence of ischemic heart disease was shown by coronary arteriography or documented myocardial infarction. Patients were classified as having dilated cardiomyopathy if normal coronary arteries had been demonstrated on coronary angiography. The cachectic group did not differ significantly from the noncachectic group with respect to age (71 ± 13 vs 67 ± 8 years, $P = .07$) and New York Heart Association class (2.9 ± 0.7 vs 2.6 ± 0.6, $P = .08$) and had a lower body mass index (21 ± 2 kg/m^2 vs 28 ± 4 kg/m^2, $P < .0001$).

No patient had uncorrected hemodynamically significant valvular disease, myocardial infarction within the previous 12 weeks, chronic lung disease, neuromuscular disorders, or severe kidney failure. The medical regimens of all the enrolled patients were optimized and all were symptomatically stable. Medications included angiotensin-converting enzyme inhibitors, diuretics, nitrates, digitalis, β-blockers, and aspirin or warfarin in varying combinations. No significant differences in medication were found between cachectic and noncachectic patients.

In the documentation of weight loss for the detection of cachexia, special care was taken that no patient had peripheral or pulmonary edema, significantly elevated jugular venous pressure, hepatomegaly, or ascites at the time of assessment. The noncachectic patients had no history of significant nonedematous weight loss in the 2 years before the study.

Procedures

Simultaneous Doppler echocardiograms and phonocardiograms were recorded along with standard lead II of the electrocardiogram, with the patient supine and in the left semilateral position. All patients were studied at rest and during quiet respiration.

Echocardiograms were recorded with the use of a Hewlett-Packard Sonos 1500 echocardiograph with a 2.5-MHz transducer (Andover, Mass). The pattern of LV wall motion was assessed from standard left parasternal and apical views. Systolic and diastolic LV dimensions, septal thickness, and posterior wall thickness were measured from the M-modes of the LV minor axis obtained with the cursor by the tips of mitral valve leaflets, with the use of leading-edge methodology. End-diastole was taken as the onset of the q wave of the simultaneously recorded electrocardiogram and end-systole as the onset of the aortic component of the second heart sound (A_2) on the phonocardiogram. All Doppler cardiographic recordings were made at a paper speed of 100 millimeters per second. The LV mass was calculated from Penn convention criteria.[18] Left ventricular fractional shortening was estimated as the percentage of decrease in dimension during ejection with respect to end-diastolic dimension. Posterior wall thickening fraction was calculated as the percentage of increase in end-systolic wall thickness with respect to end-diastolic thickness. From the long-axis traces, the total amplitude of long-axis excursion was determined at the left, septal, and right sites, and the mean mitral ring movement was calculated. Left ventricular isovolumic relaxation time was measured as the time interval from the A_2 to the onset of mitral cusp separation on the M-mode trace. From the transmitral pulsed-Doppler trace, peak early (E) and late (A) diastolic filling velocities were measured and the E/A ratio was calculated. Mitral E-wave deceleration time was measured from the peak of the E wave to its end.

Phonocardiograms were recorded from the right or left sternal edge, with the use of a medium- or high-frequency filter, in the position where A_2 was most obvious, checked against aortic valve closure artifact on pulsed Doppler record of aortic flow.

Changes in measurements of LV performance over time

To assess the changes in measurements of LV cavity size, mass, and function over time, before the index assessment, all available previous echocardiographic recordings performed in our laboratory were also analyzed. Eighteen cachectic and 35 noncachectic patients included in the study were identified as having had a previous echocardiographic examination ≥6 months before the index assessment (mean follow-up time 24 ± 15 months). The reproducibility of the echocardiographic overall LV performance in our laboratory has been described previously.[19]

Statistical analysis

Descriptive values are expressed as mean ± SD for cross-sectional parameters and mean ± SEM for changes over time within patients groups. The unpaired Student t test, Mann-Whitney U test, and χ^2 test were used when appropriate. For all tests, a P value of $<.05$ was considered statistically significant. The reproducibility of LV mass assessments with the use of echocardiography is limited. Therefore, for the assessment of changes over time in LV mass, we focused on the determination of a definite state of LV mass increase (>20%) or a state of LV mass decrease (>20%). Statistical analysis was performed with a standard statistical program package (StatView, version 4.5, Abacus Concepts Inc, Berkely, Calif).

Results

Chamber size, dimensions, and systolic function

Left ventricular and left atrial size did not differ between the 2 groups, although LV dimensions were

Table I. M-mode echocardiographic measurements and left ventricular systolic function in the two patient groups with and without cardiac cachexia (mean ± SD)

	Cachectic (n = 28)	Noncachectic (n = 56)	P
Left ventricular end-diastolic diameter (mm)	69 ± 9	67 ± 13	.43
Left ventricular end-systolic diameter (mm)	58 ± 11	55 ± 15	.35
Interventricular septal thickness (mm)	12 ± 3	13 ± 3	.11
Left ventricular posterior wall thickness (mm)	11 ± 2	12 ± 2	.4
Left ventricular mass (g)	480 ± 180	495 ± 190	.73
Left atrial dimension (mm)	48 ± 9	46 ± 8	.56
Left ventricular fractional shortening (%)	16 ± 10	19 ± 10	.23
Left ventricular posterior wall thickening (%)	53 ± 19	60 ± 15	.37
Mean mitral ring movement (mm)	8 ± 3	9 ± 3	.25

Table II. Left ventricular diastolic function in the two patient groups (mean ± SD)

	Cachectic (n = 28)	Noncachectic (n = 56)	P
M-mode measurements			
Isovolumic relaxation time (ms)	29 ± 22	36 ± 27	.26
Doppler measurements			
Peak E diastolic filling velocity (m/s)	0.7 ± 0.3	0.8 ± 0.3	.71
Peak A diastolic filling velocity (m/s)	0.4 ± 0.2	0.4 ± 0.3	.86
E/A ratio	2.7 ± 1.6	3.3 ± 2.9	.31
E-wave deceleration time (ms)	73 ± 37	76 ± 26	.77

slightly greater in the cachectic patients (Table I). Minimal differences were found in interventricular septal thickness ($P = .11$) and posterior ($P = .40$) wall thickness and LV mass between the 2 groups with and without cachexia, but LV mass was almost identical in both study groups ($P = .73$). Similarly, LV function assessed by percent fractional shortening, the rate of posterior wall thickening, and the mean mitral ring movement did not differ. Left ventricular fractional shortening was lower (16% ± 10% vs 19% ± 10%) in patients with cardiac cachexia, but this difference did not achieve statistical significance ($P = .23$). This lower average value was due to slightly greater end-diastolic and end-systolic diameters among the cachectic patients and not to markedly lower values for percent fractional shortening in a few subjects.

Diastolic function

Left ventricular diastolic function assessed by the Doppler pattern of LV inflow and E-wave deceleration time was also similar in the cachectic and noncachectic groups (Table II). Isovolumic relaxation time was slightly lower in cachectic patients (29 ± 22 ms vs 36 ± 27 ms), indicating that left atrial pressure and LV filling pressure were slightly higher in these patients. Nevertheless, this difference was statistically nonsignificant ($P = .26$), and no other variables suggested specific diastolic abnormalities in patients with cardiac cachexia.

Changes in measurements of LV performance over time

There were no consistent changes in LV size, mass, and function from the previous examination to the index examination in the patient population as a whole, though the direction of changes differed between cachectic (n = 18) and noncachectic (n = 35) patients (Table III). Although the measurements of LV size and mass remained stable or slightly increased during the time interval between the previous and index examinations in the noncachectic group, these variables had a consistent negative direction in the cachectic group (Table IV). The differences in change over time between the groups with and without cachexia achieved statistical significance in terms of LV end-diastolic diameter and were the strongest for changes in LV mass (Figure 1). By focusing on the determination of definite LV mass increase (>20%) or a state of definite LV mass decrease (>20%), we found an increase in LV mass in 2 (11%) cachectic and 14 (40%) noncachectic patients, stable LV mass in 7 cachectic and 13 noncachectic patients, and a decrease in LV mass in 9 (50%) cachectic and 8 (23%) noncachectic patients (χ^2 test, $P < .05$).

Table III. Measurements of left ventricular cavity size and mass at index and previous examinations and absolute changes in variables during time interval between the two examinations (mean ± SEM)

	Previous examination	Index examination	Absolute changes
LVEDD (mm)			
Cachectic	73 ± 2	68 ± 3	−5 ± 2
Noncachectic	64 ± 2	66 ± 2	1 ± 2
LVESD (mm)			
Cachectic	62 ± 3	58 ± 3	−4 ± 2
Noncachectic	53 ± 2	52 ± 2.	1 ± 2
IVST (mm)			
Cachectic	12.4 ± 0.5	12.4 ± 0.6	0.1 ± 0.6
Noncachectic	12.5 ± 0.4	12.8 ± 0.4	0.4 ± 0.4
LVPWT (mm)			
Cachectic	11.3 ± 0.4	10.6 ± 0.6	−0.7 ± 0.5
Noncachectic	11.3 ± 0.3	11.3 ± 0.3	0.1 ± 0.3
LV mass (g)			
Cachectic	540 ± 45	455 ± 40	−80 ± 45
Noncachectic	430 ± 25	460 ± 30	35 ± 25

LV, Left ventricular; *LVEDD*, LV end-diastolic dimension; *LVESD*, LV end-systolic diameter; *IVST*, interventricular septal thickness; *LVPWT*, LV posterior wall thickness.

Table IV. Percent changes in measurements of left ventricular cavity size and mass during time interval between previous and index examinations (mean ± SEM)

	Cachectic (n = 18)	Noncachectic (n = 35)	P
Left ventricular end-diastolic diameter (%)	−6 ± 3	3 ± 3	<.05
Left ventricular end-systolic diameter (%)	−6 ± 3	3 ± 5	.2
Interventricular septal thickness (%)	1 ± 5	5 ± 4	.53
Left ventricular posterior wall thickness (%)	−6 ± 4	2 ± 3	.12
Left ventricular mass (%)	−11 ± 7	11 ± 6	<.03

Discussion

The current study failed to detect any specific cardiac abnormalities in patients with cachectic CHF compared with patients with noncachectic CHF when assessed in a cross-sectional study. Neither measurements of cardiac dimensions and mass nor measurements of LV systolic and diastolic function differed significantly between the 2 study groups with and without cachexia. However, when these patients were followed for a mean of 24 months, changes in ventricular mass and transverse cavity diameter were observed, which differed in direction in patients with cardiac cachexia compared with noncachectic patients. In the group of patients as a whole, none of the measurements showed any significant change. Nevertheless, in individuals, a significant loss of LV mass over time occurred more frequently in cachectic patients compared with noncachectic patients, strongly suggesting that neither change was simply random or the result of measurement error but rather that such continuous evolution should be considered as part of the natural history of the disease.

Previous studies

The phenomenon of cardiac cachexia has been recognized for many centuries.[1] The entity "cachectic heart," first described in 1968 by Burch et al[17] as an acquired pathologic decrease in size, mass, and fat content of the heart, was of central importance in explaining the pathogenesis of cardiac cachexia. The role of reduced blood flow to the tissues was further developed by Pittman and Cohen,[6] who proposed that generalized cellular hypoxia is of central importance to the pathogenesis of the syndrome of cardiac cachexia. It results in poor oxidative metabolism in muscle with subsequent reduced ATP production that depresses protein synthesis.[20] They also suggested that cellular hypoxia initiates catabolism or inhibits anabolism.[6]

Several subsequent studies questioned the importance of the changes in the heart itself in the genesis of cardiac cachexia, indicating the role of severe anorexia[21] and of altered lipid metabolism.[22] Ansari[23] described 2 different syndromes of cardiac cachexia and of the cachectic heart. He also proposed the presence of pedal edema, cardiac size, and QRS voltage on

serial electrocardiography as the most important clues in the differential diagnosis of these 2 syndromes.[23] The syndrome of cardiac cachexia within CHF has subsequently received little attention.[24]

Current studies

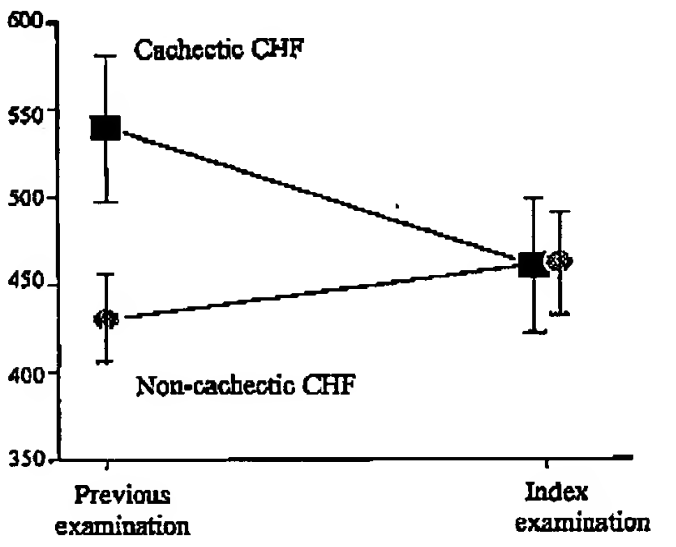
Although the reasons for loss of muscle remain unclear, CHF is regarded as a catabolic state with cytokine production,[10-13,25,26] insulin resistance,[27] and an abnormal ratio of catabolic to anabolic steroids.[28] The syndrome of cardiac cachexia is currently shown to be closely related to neurohormonal activation[9] and metabolic alterations.[14-16,29] The increasing evidence of these "noncardiac" factors raise the question of the importance of alterations in cardiac structure and function in this syndrome.

Current study

It is generally accepted that worsening of heart failure is associated with an increase in LV size and mass, and this is confirmed in our noncachectic subgroup of patients. Whether this can be expanded to cachectic heart failure has not been investigated previously. In our study, no significant differences in LV mass were found between cachectic and noncachectic patients both at the time of previous examination and of index examination. However, when monitoring these patients, significant difference in changes in this variable over time were noticed. Although echocardiography has some limitations in estimating LV mass, this difference was proved by the significant difference in changes over time in LV diastolic cavity diameter and by the observed trend in differences in changes over time in the ventricular posterior wall thickness (Table IV). The logical time sequence of events to explain these findings can be that the patients were analyzed at the time when noncachectic patients on average would still have an increase in LV mass over time and cachectic patients were on average loosing LV mass.

The pathogenesis of cardiac cachexia has yet to be elucidated, and the role of the heart in this syndrome remained obscure until evidence emerged that cachectic patients have high circulating levels of tumor necrosis factor.[10] This cytokine causes many of the clinical features of cachexia, and its production is increased in patients with a variety of neoplastic, infective, and collagen disorders characterized by muscle wasting and malnutrition.[30] In the study of Ansari,[23] the syndrome of cachectic heart was described apart from the syndrome of cardiac cachexia, implying different pathogenetic mechanisms in these syndromes. In our study, the reduction in body weight occurred in parallel to the wasting of LV mass, indicating a common mechanism. Possibly, the neurohormonal activation[31] that accompanies the failing heart could induce a variety of "peripheral" alterations, including abnormalities of the skeletal muscle and metabolic impairment. When the sum of these factors reach a threshold, a cascade of secondary vicious circles are initiated, leading to skeletal and cardiac muscle wasting and cachexia.

Figure 1



Dynamics of left ventricular mass over time in patients with and without cachexia. ΔLV mass in cachectic patients versus ΔLV mass in noncachectic patients, $P < .03$.

Limitations

Retrospective data were used to assess the changes in measurements of LV performance over time, though all measurements were performed by a single experienced observer who was unaware of patient details and group assignment. The individual measurements we made, particularly in LV cavity size and mass, will have been subject to measurement error, a problem compounded when small differences between those made on 2 occasions several months apart were derived. This effect was minimized by use of identical equipment and techniques on both occasions. Although all patients were receiving standard medications, treatment was individualized and was thus not uniform throughout the group of patients studied, and most of the patients were studied before β-blockers were included in standard therapy. We are thus unable to determine whether their use would have altered dynamics of LV size and mass over time. Finally, measurements in individual patients were made on only 2 occasions, so we cannot say whether these changes

are consistent or subject to longer-term variability in their direction or magnitude.

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References

1. Katz AM, Katz PB. Diseases of heart in works of Hippocrates. Br Heart J 1962;24:257-64.
2. Anker SD, Coats AJ. Cardiac cachexia: a syndrome with impaired survival and immune and neuroendocrine activation. Chest 1999; 115:836-47.
3. Wilson JR, Martin JL, Schwartz D, et al. Exercise intolerance in patients with chronic heart failure: role of impaired nutritive flow to skeletal muscle. Circulation 1984;69:1079-87.
4. Clark A, Volterrani M, Swan JW, et al. Leg blood flow, metabolism and exercise capacity in chronic stable heart failure. Int J Cardiol 1996;55:127-35.
5. Gibson JN, Halliday D, Morrison WL, et al. Decrease in human quadriceps muscle protein turnover consequent upon leg immobilisation. Clin Sci 1987;72:503-9.
6. Pittman JA, Cohen P. The pathogenesis of cardiac cachexia. N Engl J Med 1964;271:403-8.
7. Abel RM, Fisher J, Buckley MJ, et al. Malnutrition in cardiac surgical patients. Arch Surg 1976;111:45-50.
8. Carr JG, Stevenson LW, Walden JA, et al. Prevalence and hemodynamic correlates of malnutrition in severe congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 1989;63:709-13.
9. Anker SD, Chua TP, Ponikowski P, et al. Hormonal changes and catabolic/anabolic imbalance in chronic heart failure and their importance for cardiac cachexia. Circulation 1997;96:526-34.
10. Levine B, Kalman J, Mayer L, et al. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. N Engl J Med 1990;323:236-41.
11. McMurray J, Abdullah I, Dargie HJ, et al. Increased concentrations of tumor necrosis factor in "cachectic" patients with severe chronic heart failure. Br Heart J 1991;66:356-8.
12. Anker SD, Egerer KR, Volk HD, et al. Elevated soluble CD14 receptors and altered cytokines in chronic heart failure. Am J Cardiol 1997;79:1426-30.
13. Dutka DP, Elborn JS, Delomere F, et al. Tumor necrosis factor in severe congestive cardiac failure. Br Heart J 1993;70:141-3.
14. Rauchhaus M, Carroll PV, Russel-Jones D, et al. Body wasting in chronic heart failure is associated with altered fat and protein metabolism [abstract]. J Am Coll Cardiol 1999;33(A Suppl):171.
15. Leyva F, Anker SD, Egerer K, et al. Hyperleptinaemia in chronic heart failure, relationships with insulin. Eur Heart J 1998;19:1547-51.
16. Anker SD, Clark AL, Teixeira MM, et al. Loss of bone mineral in patients with cachexia due to chronic heart failure. Am J Cardiol 1999;83:612-5.
17. Burch GE, Phillips JH, Ansari A. The cachectic heart, a clinicopathologic, electrocardiographic and roentgenographic entity. Chest 1968;54:403-9.
18. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man: anatomic validation of the method. Circulation 1979;59:623-32.
19. Henein MY, Amadi A, O'Sullivan C, et al. ACE inhibitors unmask incoordinate diastolic wall motion in restrictive left ventricular disease. Heart 1996;76:326-31.
20. Morrison WL, Gibson NA, Rennie MJ. Skeletal muscle and whole body protein turnover in cardiac cachexia: influence of branched chain amino acid administration. Eur J Clin Invest 1988;75:415-20.
21. Buchanan N, Kaan RD, Kingsley R, et al. Gastrointestinal absorption studies in cardiac cachexia. Intensive Care Med 1977;3:89-91.
22. Bobkova VI, Fomchenkov SI. Pathogenesis of cachexia in cardiac insufficiency [in Russian]. Kardiologiia 1975;15:22-5.
23. Ansari A. Syndromes of cardiac cachexia and the cachectic heart: current perspective. Prog Cardiovasc Dis 1987;30:45-60.
24. Ferrari R. The importance of cachexia in the syndrome of heart failure [editorial]. Eur Heart J 1997;18:187-9.
25. Zhao SP, Zeng LH. Elevated plasma levels of tumor necrosis factor in chronic heart failure with cachexia. Int J Cardiol 1997;58:257-61.
26. Doyama K, Fujiwara W, Fukumoto M, et al. Tumour necrosis factor is expressed in cardiac tissues of patients with heart failure. Int J Cardiol 1996;54:217-25.
27. Swan JW, Anker SD, Walton C, et al. Insulin resistance in chronic heart failure: relationship to severity and etiology of heart failure. J Am Coll Cardiol 1997;30:527-30.
28. Anker SD, Clark AL, Kemp M, et al. Tumor necrosis factor and steroid metabolism in chronic heart failure: possible relation to muscle wasting. J Am Coll Cardiol 1997;30:997-1001.
29. Morrison WL, Edwards RHT. Cardiac cachexia. BMJ 1991;302: 301-2.
30. Packer M. Is tumor necrosis factor an important neurohormonal mechanism in chronic heart failure? Circulation 1995;92:1374-82.
31. Packer M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. J Am Coll Cardiol 1992;20:248-54.

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Wasting of the left ventricle in patients with cardiac cachexia: a cardiovascular magnetic resonance study

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Abstract

Background: The "cachectic heart" has been described as a pathologic decrease in the size and mass of the heart, but no in vivo studies have shown changes in cardiac dimensions or left ventricular (LV) mass over time in chronic heart failure (CHF) associated with body wasting (cardiac cachexia). Cardiovascular magnetic resonance (CMR) has high reproducibility and is more sensitive than other techniques. *Methods:* CMR studies of LV volumes and mass were performed at baseline and a mean of 15 months later in nine CHF patients with cardiac cachexia and 28 matched CHF controls without cachexia (mass index 23 ± 1 vs. 29 ± 5 kg/m^2, P=0.0005). *Results:* At baseline, LV end-diastolic volume (197 ± 78 vs. 203 ± 65 ml), end-systolic volume (131 ± 75 vs. 126 ± 63 ml), LV mass (213 ± 44 vs. 222 ± 62 g), and LV ejection fraction (38 ± 19% vs. 40 ± 16%) did not differ between cachectic patients and controls (all P>0.10). During follow-up, there was a significant decrease in LV mass in patients with cachexia (− 16 g, P<0.05) and a trend to increase in LV mass in patients without cachexia (+7 g, P= 0.12, comparison between groups: P= 0.010). *Conclusions:* The direction of changes over time in LV mass differs in CHF patients with cachexia as compared with non-cachectic controls. A significant decrease in LV mass occurs in patients with cardiac cachexia. This study documents in vivo the occurrence of wasting of the left ventricle in patients with CHF who demonstrate general body wasting.

Keywords: Heart failure; Cardiac cachexia; Left ventricular mass; Magnetic resonance imaging

1. Introduction

Longstanding severe chronic heart failure (CHF) is often accompanied by a loss of fat, lean and bone mass [1,2], and when the wasting process leads to weight loss it is termed "cardiac cachexia". It has been recognised since the classical description by Hippocrates, and is associated with a particularly adverse prognosis [3]. Although the "cachectic heart" has been described as a pathologic decrease in the size and mass of the heart [4], and although some patients may be shown to lose cardiac mass [5], no study has shown consistent in vivo changes in cardiac dimensions or ventricular mass over time in CHF patients with cardiac cachexia. The purpose of this investigation was to assess prospectively, using highly reproducible cardiovascular magnetic resonance (CMR) techniques, the left ventricular (LV) dimensions, mass and function and the direction and magnitude of changes in these measurements over time in patients with CHF with and without cachexia.

2. Methods

2.1. Patient population and characteristics

The study was performed during the time interval between September 1999 and March 2000. The target population for this study was all cachectic CHF patients (see below for definitions) of ischemic or dilated cardiomyopathy origin, referred for CMR examination as part of their

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routine assessment at the Royal Brompton Hospital between April 1998 and May 1999 (index time period). A total of nine consecutive patients with cardiac cachexia were identified physically present at the study time period, with no contraindications for the repeated CMR and willing to participate into the study. These patients (all men, age 50–87 years, duration of heart failure prior to first CMR scan: 10 ± 6 years) had documented non-edematous and non-intentional weight loss of more than 7.5% over a period of more than 6 months prior to the first CMR scan, according to our previous definition of cardiac cachexia [6]. We also aimed to recruit a group of non-cachectic CHF patients of the same age and heart failure etiology to match the cachectic patients in a 1:3 ratio who also had undergone a CMR during the index time period. This group comprised 28 patients with non-cachectic CHF (24 men and four women, age 50–79 years, duration of heart failure prior to first CMR scan: 11 ± 7 years).

The total number of CHF patients who had a CMR scan during the index period was 77 (cachectic: 11 [14%]). Subsequently, three patients died, one patient received a pacemaker, four patients were unstable at the time of being considered for the second study. Three patients declined to participate in the study (no reason stated: two; because of claustrophobia: one). Thus, of 11 patients with cardiac cachexia at the index visit we have restudied nine, and of the remaining 66 non-cachectic patients we have restudied 28. We report on the 37 patients who agreed to participate in the study and had two CMR scans.

The primary end point of the study was the comparison of the changes in LV mass over time between patients with and without cardiac cachexia, on the a priori assumption that non-cachectic patients would demonstrate an increase in LV mass with time, whereas cachectic patients would demonstrate a reduction due to progressive cardiac wasting.

According to our previous findings, CMR requires nine patients with heart failure to detect a 10 g change in LV mass over time with a statistical power of 90% and an α-error of 0.05 [7]. This sample size takes into consideration the intra-observer (2–7%) and inter-study (2–5%) reproducibility of CMR data in patients with CHF, tested in our laboratory [7].

We took the European Society of Cardiology guidelines definition that the diagnosis of heart failure would be made if both of the following were present: symptoms compatible with a diagnosis of heart failure, mainly exertional breathlessness for at least 6 months, and evidence of substantial impairment of LV systolic function or LV filling on Doppler echocardiography [8]. CHF was of ischemic origin in four (44%) cachectic patients and in 14 (50%) non-cachectic patients. The presence of ischemic heart disease was shown either by coronary angiography or documented myocardial infarction. Patients were classified as having dilated cardiomyopathy if normal coronary arteries had been demonstrated on coronary angiography. The cachectic group did not differ significantly from the non-cachectic group with respect to age (69 ± 12 vs. 65 ± 9 years, $P=0.20$), but they demonstrated, as expected, a lower body mass index (23 ± 1 vs. 29 ± 5 kg/m^2, $P=0.0005$).

At the time of investigation, all patients were clinically stable and were regular outpatient attendees. No patients had clinical signs of acute infection or other primary cachectic conditions (such as cancer, thyroid disease, or severe liver disease), none had residual signs of peripheral or pulmonary edema, and were studied when free of ascites. No patients with hemodynamically important valve disease, significant primary pulmonary disease, neuromuscular disorders, myocardial infarction within the previous 6 months, renal failure, peripheral vascular disease, or excessive alcohol intake were included into the study. The medical regimens of all the enrolled patients had been optimised by our heart failure clinic prior to study and they were all symptomatically stable. Standardized medical treatment between the first and second examinations included angiotensin converting enzyme inhibitors (92% of patients), diuretics (97% of patients), nitrates (27% of patients), digitalis (24% of patients), beta-blockers (11% of patients) and aspirin or warfarin (86% of patients) in varying combinations. No significant differences in medication were found between cachectic and non-cachectic patients. The study protocol was approved by the Ethics Committee of the Royal Brompton Hospital, London. All patients gave written informed consent.

2.2. Cardiovascular magnetic resonance

All subjects were imaged using a Picker Edge 1.5 T scanner (Picker, Cleveland, OH, USA). LV volumes were determined by the use of contiguous breath hold short

Table 1
LV dimensions, mass, and ejection fraction in the two groups of patients with and without cachexia at the baseline and follow-up evaluations (mean ± S.D.)

	Visit	Cachectic ($n=9$)	Non-cachectic ($n=28$)	Mean difference	P-value
EDV (ml)	Baseline	197 ± 78	203 ± 65	−6	0.83
	Follow-up	193 ± 86	202 ± 72	−9	0.75
ESV (ml)	Baseline	131 ± 75	126 ± 63	4	0.86
	Follow-up	126 ± 84	129 ± 69	−2	0.93
SV (ml)	Baseline	66 ± 18	76 ± 24	−10	0.25
	Follow-up	66 ± 14	73 ± 22	−7	0.41
EF (%)	Baseline	38 ± 19	40 ± 16	−3	0.67
	Follow-up	41 ± 21	40 ± 16	1	0.92
LV mass (g)	Baseline	213 ± 44	222 ± 62	−9	0.70
	Follow-up	197 ± 36*	229 ± 62	−32	0.16
LV mass/ weight (g/kg)	Baseline	3.30 ± 0.82	2.55 ± 0.69	0.75	0.01
	Follow-up	3.01 ± 0.65*	2.64 ± 0.68†	0.36	0.17

EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; EF, ejection fraction; LV mass, left ventricular mass. *$P<0.05$ and †$P=0.10$ between follow-up and baseline examination.

Table 2
Absolute and percent changes in measurements of LV cavity size and mass during the time interval between the baseline and follow-up examinations (mean ± S.E.)

		Cachectic (n=9)	Non-cachectic (n=28)	Mean difference	P-value
Δ EDV	ml	−4 ± 12	−1 ± 5	−3	0.77
	%	−7 ± 10	−3 ± 3	−4	0.55
Δ ESV	ml	−4 ± 11	2 ± 4	−7	0.44
	%	−21 ± 21	−2 ± 4	−19	0.14
Δ LV mass	g	−16 ± 7	7 ± 4	−23	0.010
	%	−8 ± 3	3 ± 2	−11	0.007
Δ LV mass/ weight	g/kg	−0.29 ± 0.12	0.09 ± 0.05	−0.38	0.002
	%	−8 ± 3	4 ± 2	−12	0.008

Δ, changes over time; EDV, end-diastolic volume; ESV, end-systolic volume; LV mass, left ventricular mass.

axis cines from the mitral valve orifice to the LV apex [9,10]. Care was taken to position the first slice on the atrioventricular valve plane, and subsequent slices were acquired moving towards the apex. Ten to 14 10-mm thick slices were required to cover the ventricle. Imaging time was typically 30 min. The images were analysed using in-house developed software (CMRtools©, Imperial College London, UK). A single independent operator (J.M.) analysed all the images, and he was blinded to the clinical details of the patient and the study date. Although it is not possible to blind the images to body size, the images were presented in random sequence. A fixed set of criteria for the determination of borders was used, and both scans from each patient were analysed side-by-side to minimise inter-study variation [7]. Endocardial and epicardial contours in diastole and endocardial contours in systole were drawn manually and end-diastolic, end-systolic and LV myocardial tissue volumes were calculated by summation. The LV mass was calculated by multiplying the myocardial tissue volume by the myocardial specific density of 1.05 g/cm^3.

2.3. Statistical analysis

Descriptive values are expressed as mean ± S.D. for cross-sectional variables and mean ± S.E. for changes over time within patients groups. A paired Student's t-test, was used to compare the results of the first and second assessments. Differences between group means were compared by unpaired t-test and Mann–Whitney U-test. For all tests, a P-value less than 0.05 was considered statistically significant. Statistical analysis was performed using a standard statistical program package (StatView, version 5.0, Abacus Concepts Inc., Berkeley, CA).

3. Results

A summary of the LV hemodynamic data at the baseline and follow-up examinations for both groups of CHF patients with and without cardiac cachexia is presented in Table 1. By definition, at the baseline examination, the left ventricle was dilated in both groups of patients [9]. At baseline the LVEF was decreased and the LV mass was increased to a similar degree in cachectic and non-cachectic patients, respectively.

During the follow-up period between the two CMR examinations, which averaged 17 months for the cachectic group and 15 months for the non-cachectic group (P=0.16), LV dimensions, stroke volume, and ejection fraction showed no significant change in either group of patients (Table 2). In the two study groups blood pressure was similar at baseline (P=0.5) and did not change during follow-up (P>0.2). Also, body weight remained stable during follow-up

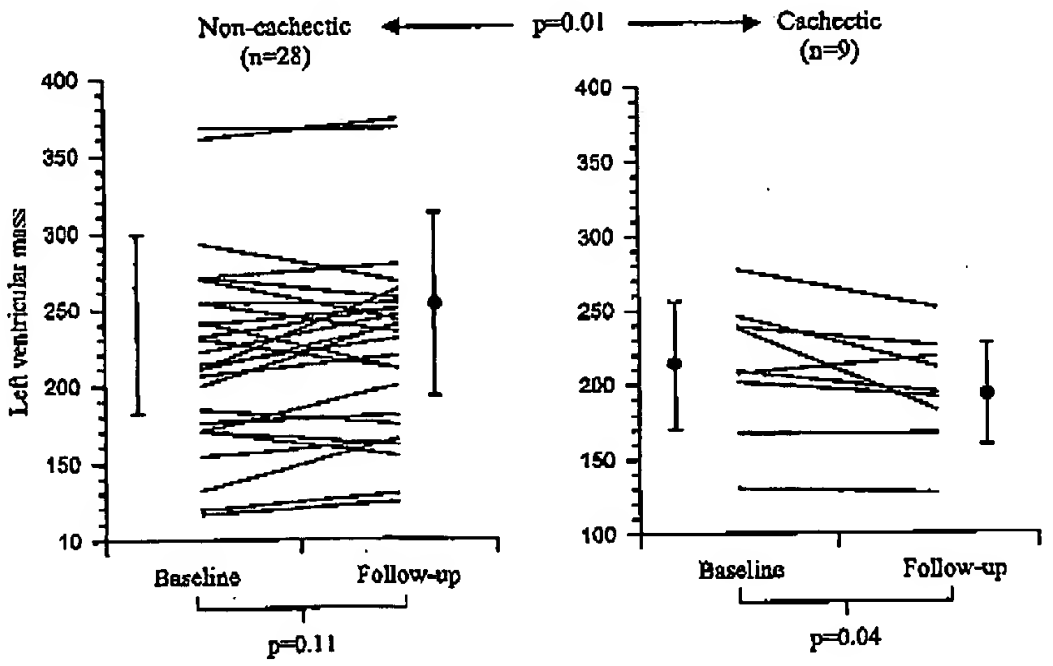

Fig. 1. Change in LV mass from baseline to end of follow-up for patients with and without cachexia. Vertical bars denote 1 S.D. above and below the mean.

(cachectics: 65.3–66.2 kg; non-cachectic patients 87.8–87.6 kg). However, analysing changes over time, we found a significant decrease in LV mass in cachectic patients (-16 ± 7 g, $P=0.04$) and a borderline increase in LV mass in non-cachectic patients ($+7 \pm 4$ g, $P=0.12$). As illustrated in Fig. 1, the direction and magnitude of changes in LV mass over time were significantly different in patients with and without cardiac cachexia ($P=0.010$ for t-test as well as Mann–Whitney U-test).

4. Discussion

The main result of this study is that the syndrome of cardiac cachexia is associated with wasting of the left ventricle. In contrast to CHF patients without cachexia, in whom LV mass tends to increase further over time, patients with cardiac cachexia show a significant decrease of LV mass during follow-up. These findings were demonstrated in vivo using the CMR, which is the most sensitive and reproducible technique for LV mass estimation currently available [11], and significantly superior to 2D echocardiography [12]. Our sample size calculation shows that we used a sufficiently large patient population to demonstrate significant change in LV mass, and CMR has thus proven to be more sensitive to remodelling changes compared to our previously published results with 2D echocardiography [5]. Changes in LV mass, either up or down, should be considered as part of the natural history of the CHF syndrome, and these changes might suggest different pathophysiological mechanisms to be operative in patients at different stages of their disease.

It is generally accepted that worsening of heart failure is associated with ventricular remodelling and increasing LV mass [7], and this is confirmed in our non-cachectic subgroup of patients. Whether this can be expanded to cachectic heart failure has not previously been investigated. In our study, no significant differences in LV mass were found between cachectic and non-cachectic patients at baseline. However, when monitoring these patients, significant difference in changes in this variable over time were noticed. A possible explanation for these findings is that the patients were analysed at the time when non-cachectic patients on average were still increasing LV mass and cachectic patients were on average losing LV mass.

A number of possible mechanisms might underlie the reduction of LV mass in heart failure patients with cardiac cachexia. It is now commonly recognized that progressive LV dysfunction occurs, in part, as a result of apoptosis [13,14]. The importance of this type of cell death in cardiac failure is not yet firmly established. Questions remain as to whether apoptosis is a cause or a consequence of heart failure. Apoptosis was shown to be associated with the increased myocardial stretch in pressure-overload-induced hypertrophy [15] and to occur at an increased rate and after injury due to ischemia or reperfusion [14,16]. Other well-known triggers of apoptosis include cytokines, oxidative stress and mitochondrial damage [17,18]. Patients with severe CHF and particularly with cachexia have been shown to have high circulating levels of tumour necrosis factor [19] and other inflammatory cytokines [20]. Tumour necrosis factor causes many of the clinical features of cachexia, and its production is increased in patients with a variety of neoplastic, infective and collagen disorders characterised by muscle wasting and malnutrition [21]. TNF is expressed in the heart of patients with severe heart failure [22]. Apoptosis may result, and this could explain the reduction in LV mass in cachectic CHF patients.

Different loading conditions, particularly left atrial pressure and LV afterload, might conceivably be involved in the changes in LV cavity size and mass over time. Underfilling of the ventricle or an increase in left atrial pressure, possibly as the result of inappropriate diuretic therapy, might cause changes in LV cavity size [23]. Decreased LV afterload was associated with a reduction in LV mass in an echocardiographic study of anorexia nervosa [24]. In our study, the reduction in LV mass in cachectic patients was not associated with any changes in LV dimensions and ejection fraction. The blood pressure was also similar in the two study groups at baseline, and did not change significantly during follow-up.

Remodeling of the ventricle, clinically manifested as changes in size, shape and function of the heart after cardiac injury [25], is another important mechanism underlying the progression of heart failure [26]. It is a process that is common to multiple heart failure etiologies [27], which can be delayed or even reversed by appropriate treatment [28,29]. Our patients were on stable therapy and there were no significant differences in medication between the two groups. The reduction in LV mass in the cachectic group was not accompanied with a similar reduction in the ventricular cavity size, thus further decreasing the LV mass to volume ratio and further distorting the overall geometry of the ventricle, which is an independent prognostic marker in these patients [30].

4.1. Study limitations

The individual measurements we made in LV cavity size and mass will have been subject to measurement error, a problem compounded when small differences between those made on two occasions several months apart were derived. To minimise this effect, identical equipment and standard guidelines were used on both occasions, and all the images were analysed by the same investigator, blinded to the clinical details of the patient and the CMR study date. The LVEF appears to be relatively high in the patients studied here, but it has been recognised that CMR generally derives higher (and more accurate) LVEFs than echocardiography [31]. Indeed, the LVEF by radionuclide ventriculography was available in seven (of nine) cachectic and in 26 (of 28) non-cachectic CHF patients included into this

study and averaged 30 ± 10% and 33 ± 16% in the cachectic and non-cachectic subgroups, respectively ($P=0.49$). Although all patients were on standard medications, treatment was individualised and was thus not uniform throughout the group of patients studied. Finally, measurements in individual patients were made on only two occasions, so we cannot say whether these changes are consistent or subject to longer term variability in their direction or magnitude. However our study is supported by our previously published echocardiography follow-up study [5].

5. Conclusions

The direction of changes over time in LV mass differs in CHF patients with cachexia as compared to those without cachexia. A significant decrease in LV mass occurs in patients with cardiac cachexia. This study documents in vivo the occurrence of wasting of the left ventricle in patients with CHF who demonstrate general body wasting. Further studies are needed to find out the mechanisms of cardiac wasting in these patients.

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References

[1] Mancini DM, Walter G, Reichek N, Lenkinski R, McCully KK, Mullen JL, et al. Contribution of skeletal muscle atrophy to exercise intolerance and altered muscle metabolism in heart failure. Circulation 1992;85:1364–73.
[2] Anker SD, Clark AL, Teixeira MM, Hellewell PG, Coats AJ. Loss of bone mineral in patients with cachexia due to chronic heart failure. Am J Cardiol 1999;83:612–5 (A10).
[3] Anker SD, Negassa A, Coats AJS, Afzal R, Poole-Wilson PA, Cohn JN, Yusuf S. Prognostic importance of weight loss in chronic heart and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. Lancet 2003;361:1077–83.
[4] Burch GE, Phillips JH, Ansari A. The cachectic heart. A clinico-pathologic, electrocardiographic and roentgenographic entity. Chest 1968; 54:403–9.
[5] Florea VG, Henein MY, Rauchhaus M, Koloczek V, Sharma R, Doehner W, et al. The cardiac component of cardiac cachexia. Am Heart J 2002;144:43–50.
[6] Anker SD, Coats AJ. Cardiac cachexia: a syndrome with impaired survival and immune and neuroendocrine activation. Chest 1999;115: 836–47.
[7] Bellenger NG, Davies LC, Francis JM, Marcus NJ, Pennell DJ. Reduction in sample size for studies of remodelling in heart failure by the use of cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2000;2:271–8.
[8] The Task Force on Heart Failure of the European Society of Cardiology. Guidelines for the diagnosis of heart failure. Eur Heart J 1995; 16:741–51.
[9] Lorenz CH, Walker ES, Morgan VL, Klein SS, Graham TP. Normal human right and left ventricular mass, systolic function and gender differences by cine magnetic resonance imaging. J Cardiovasc Magn Reson 2000;1:7–21.
[10] Bellenger NG, Francis JM, Davies CL, Coats AJS, Pennell DJ. Establishment and performance of a magnetic resonance cardiac function clinic. J Cardiovasc Magn Reson 2000;2:15–22.
[11] Myerson SG, Bellenger NG, Pennell DJ. Assessment of left ventricular mass by cardiovascular magnetic resonance. Hypertension 2002; 39:750–5.
[12] Grothues F, Smith GC, Moon JC, Bellenger NG, Collins P, Klein HU, et al. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. Am J Cardiol 2002;90:29–34.
[13] Narula J, Haider N, Virmani R, DiSalvo TG, Kolodgie FD, Hajjar RJ, et al. Apoptosis in myocytes in end-stage heart failure. New Engl J Med 1996;335:1182–9.
[14] Olivetti G, Abbi R, Quaini F, Kajstura J, Cheng W, Nitahara JA, et al. Apoptosis in the failing human heart. New Engl J Med 1997;336: 1131–41.
[15] Cheng W, Li B, Kajstura J, Li P, Wolin MS, Sonnenblick EH, et al. Stretch-induced programmed myocyte cell death. J Clin Invest 1995; 96:2247–59.
[16] Gottlieb RA, Burleson KO, Kloner RA, Babior BM, Engler RL. Reperfusion injury induces apoptosis in rabbit cardiomyocytes. J Clin Invest 1994;94:1621–8.
[17] Ferrari R, Agnoletti L, Comini L, Gaia G, Bachetti T, Cargnoni A, et al. Oxidative stress during myocardial ischaemia and heart failure. Eur Heart J 1998;19(Suppl. B):B2–B11.
[18] Sharma R, Anker SD. Cytokines, apoptosis and cachexia: the potential for TNF antagonism. Int J Cardiol 2002;85:161–71.
[19] Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. New Engl J Med 1990;323:236–41.
[20] Bolgor AP, Anker SD. Tumour necrosis factor in chronic heart failure: a peripheral view on pathogenesis, clinical manifestations and therapeutic implications. Drugs 2000;60:1245–57.
[21] Rauchhaus M, Doehner W, Francis DP, Davos C, Kemp M, Liebenthl C, Niebauer J, Hooper J, Volk H-D, Coats AJS, Anker SD. Plasma cytokine parameters and mortality in patients with chronic heart failure. Circulation 2000;102:3060–7.
[22] Torre-Amione G, Kapadia S, Lee J, Durand JB, Bies RD, Young JB, et al. Tumor necrosis factor-alpha and tumor necrosis factor receptors in the failing human heart. Circulation 1996;93:704–11.
[23] Florea VG, Henein MY, Anker SD, Francis DP, Gibson DG, Coats AJ. Relation of changes over time in ventricular size and function to those in exercise capacity in patients with chronic heart failure. Am Heart J 2000;139:913–7.
[24] St John Sutton MG, Plappert T, Crosby L, Douglas P, Mullen J, Reichek N. Effects of reduced left ventricular mass on chamber architecture, load, and function: a study of anorexia nervosa. Circulation 1985;72:991–1000.
[25] Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling—concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. J Am Coll Cardiol 2000;35:569–82.
[26] Cohn JN. Structural basis for heart failure. Ventricular remodeling and its pharmacological inhibition. Circulation 1995;91:2504–7.
[27] Florea VG, Mareyev VY, Samko AN, Orlova IA, Coats AJ, Belenkov YN. Left ventricular remodelling: common process in patients with different primary myocardial disorders. Int J Cardiol 1999;68:281–7.
[28] Tamura T, Said S, Harris J, Lu W, Gerdes AM. Reverse remodeling of

cardiac myocyte hypertrophy in hypertension and failure by targeting of the renin-angiotensin system. Circulation 2000;102:253–9.

[29] Levin HR, Oz MC, Chen JM, Packer M, Rose EA, Burkhoff D. Reversal of chronic ventricular dilation in patients with end-stage cardiomyopathy by prolonged mechanical unloading. Circulation 1995; 91:2717–20.

[30] Douglas PS, Morrow R, Ioli A, Reichek N. Left ventricular shape, afterload and survival in idiopathic dilated cardiomyopathy. J Am Coll Cardiol 1989;13:311–5.

[31] Bellenger NG, Burgess MI, Ray SG, Lahiri A, Coats AJ, Cleland JG, et al. Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance; are they interchangeable? Eur Heart J 2000;21:1387–96.

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Ventricular assist device in severe heart failure

Effects on cytokines, complement and body weight

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Aims Inflammatory and immune activation and body wasting are important features of end-stage chronic heart failure. It is not known whether restoration of cardiac output by assist device implantation can improve these abnormalities.

Methods We studied 48 patients (39 males; age 45 ± 2 years) with NYHA class IV heart failure. All patients underwent ventricular assist device implantation for end-stage heart failure as a bridge to cardiac transplantation. Plasma levels of tumour necrosis factor α, and its receptors, interleukin-6, elastase, activated complement, and soluble CD14 receptors were measured at the time of operation and in survivors at 1 week (n=46), 40 days (n=35) and 90 days (n=26). Follow-up was for a minimum of 1 year.

Results One-year survival was 35% (95% CI: 22–49%). Body mass index was the only predictor of survival (body mass index >25 (n=16); survival 63 (39–86) %; body mass index <25 (n=32); survival 22 (7·5–36) %: P=0·003). Tumour necrosis factor α fell from 9·66 ± 1·33 pg . ml^{-1} to 4·2 ± 1·0 at 1 week (P=0·008), but returned to pre-operative levels at 90 days. Interleukin-6, activated complement and elastase fell progressively to 40 days, but were rising at 90 days. There was no change in tumour necrosis factor receptor. There was a gradual rise in CD14 (3·99 ± 0·15 μg . ml^{-1} at baseline, 5·02 ± 0·39 at 90 days, P=0·006). After surgery, body weight fell from 80 ± 2 to 73 ± 2 kg by 1 month (P<0·001) and to 72 ± 2 kg at 90 days.

Conclusions Ventricular assist device implantation results in a short-term fall in tumour necrosis factor α and interleukin-6, but no change in CD14 or tumour necrosis factor receptor, suggesting that the pathophysiological process resulting in inflammation was not altered by left ventricular assist device implantation. Low body mass index is related to poor outcome after assist device implantation, and no weight gain.
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Introduction

Key features of end-stage chronic heart failure are body wasting and inflammatory and immune activation. The origins of immune activation remain unclear, but may be related to body wasting, that is, cardiac cachexia[1,2], itself associated with a particularly poor prognosis[3].

Possible explanations for immune activation include the heart as a source of cytokines, supported by the finding that explanted failing hearts exhibit tumour necrosis factor α expression[4]. Transgenic mice with cardiac over-expression of tumour necrosis factor α develop impaired cardiac function, congestive heart failure and die prematurely[5,6]. Thus, if the heart is, indeed, the origin of immune activation, it may contribute to further deterioration in cardiac function. The potential stimulus to cardiac production of tumour necrosis factor α is not clear.

Anker *et al.* have developed an alternative hypothesis, that immune activation may be secondary to bacterial

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endotoxin exposure, perhaps as a result of repeated episodes of bowel wall oedema and subsequent translocation of bacterial products across the intestinal wall[7]. In support of this hypothesis, circulating levels of endotoxin are higher in heart failure patients with oedema, and become lower with diuretic treatment[8].

We were interested to investigate what might happen to immune activation in a group of patients with very severe heart failure who had their central haemodynamic problem corrected by the implantation of a ventricular assist device. Device implantation is itself a potentially strongly immunogenic stimulus. We measured tumour necrosis factor α and its soluble receptor, and CD14 as a measure of endotoxin–cell interaction[9]. In addition, we measured activated complement levels, and elastase as a measure of neutrophil activation[10,11]. There is no treatment at present for cachexia in chronic heart failure patients that restores normal weight. To assess the global metabolic effects of left ventricular assist device implantation, we also studied body weight changes after surgery.

Methods

We studied 48 patients at a single site who had ventricular assist devices implanted for severe cardiac failure (all New York Heart Association class IV). The indication for device implantation was end-stage heart failure or cardiogenic shock in all cases. The underlying presumption in all cases was that the patient would die without further support whilst on maximal medical therapy. The aim for each patient was that device implantation would be a bridge to transplantation. The implantations were performed between November 1992 and June 1995.

The study was approved by the ethics Committee of the Berlin Charité Hospital. Many patients were unable to give consent for the blood testing, but a relative of the patient was asked to give consent where necessary.

An ELISA was used to measure both C3a (Progen Biotechnik GmbH, Heidelberg, Germany) and C5a (Behring Werke AG, Marburg, Germany), C3a and C5a being activated complement factors 3 and 5, respectively. Elastase was measured by a commercially available ELISA test (E. Merck AG, Darmstadt, Germany). CD14 was measured by an ELISA test kit with a sensitivity 1 ng . ml^{-1} (IBL, Hamburg, Germany). Test kits from R&D Systems (Minneapolis, MN, U.S.A.) were used to measure soluble tumour necrosis factor receptor 1 (sensitivity 25 pg . ml^{-1}) and interleukin-6 (sensitivity 0·094 pg . ml^{-1}). Total tumour necrosis factor α (Medgenix, Fleurus, Belgium; lower limit of detectability 3·0 pg . ml^{-1}) was also measured. The results from this test are not influenced by soluble tumour necrosis factor receptors.

Samples were taken, separated and frozen at −80 °C for later analysis. Plasma levels of the cytokines were measured. The same sampling system was used for all patients. Samples were taken at the time of surgery (n=48), and in survivors at 1 week (n=46), 1 month (n=35) and 90 days (n=26) post-operation. Data for the cytokines measured were log transformed to achieve a normal distribution. We used Cox proportional hazard analysis with Kaplan–Meier plots to illustrate survival data. In those patients who survived at least 90 days (n=26), comparison between variables at different time slots was with a repeated measures analysis of variance, with post hoc analysis where appropriate. In order to compare data between the time slots for all subjects alive at that moment, repeated paired t-tests were used with statistical significance set at a probability of <0·01. For other statistical tests, a probability of <0·05 was taken to be statistically significant. Correlations were performed by the least squares methods. Data are presented as mean ± SD.

Table 1 Pre-operative details of patients undergoing left ventricular assist device implantation

	Patients (n=48)
Sex	Males 39; females 9
Diagnosis	DCM 37; IHD 11
Age (years)	45·3 ± 2·0
Height (cm)	176·5 ± 1·3
Weight (kg)	76·2 ± 2·2
LVEF (%)	17·5 ± 0·7
Cardiac index (l . min^{-1} . m^{-2})	1·73 ± 0·09
Heart rate (min^{-1})	122·1 ± 2·7
Mean systemic BP (mmHg)	66·5 ± 1·2
Mean pulmonary BP (mmHg)	35·3 ± 1·1

Patient data at time of implantation of ventricular assist device. DCM=dilated cardiomyopathy; IHD=ischaemic heart disease; LVEF=left ventricular ejection fraction; BP=blood pressure. Figures given are mean (± SD).

Results

Patient data at the time of surgery are shown in Table 1. There were more patients with dilated cardiomyopathy than with ischaemic heart disease. All patients were on intravenous inotropic support at the time of implantation. The duration of heart failure before assist device implantation was 3·89 ± 3·94 years (range 1 month to 13 years). Twenty-five patients had a left ventricular assist device (20 patients had a Novacor[12], five a HeartMate TCI[13]) and 23 a biventricular assist (the Berlin Heart[14]). The devices were implanted with the patient on cardiopulmonary bypass. Heparin was antagonized fully with protamine after termination of extracorporeal circulation. Intravenous heparin was started 6 to 12 h after the operation in the absence of bleeding. Patients with the Berlin Heart and Novacor were later switched to coumadine and acetylsalicylic acid was added. Patients on TCI received only acetylsalicylic acid. The HeartMate TCI left ventricular assist device implantation is distinct from the other two devices in that its

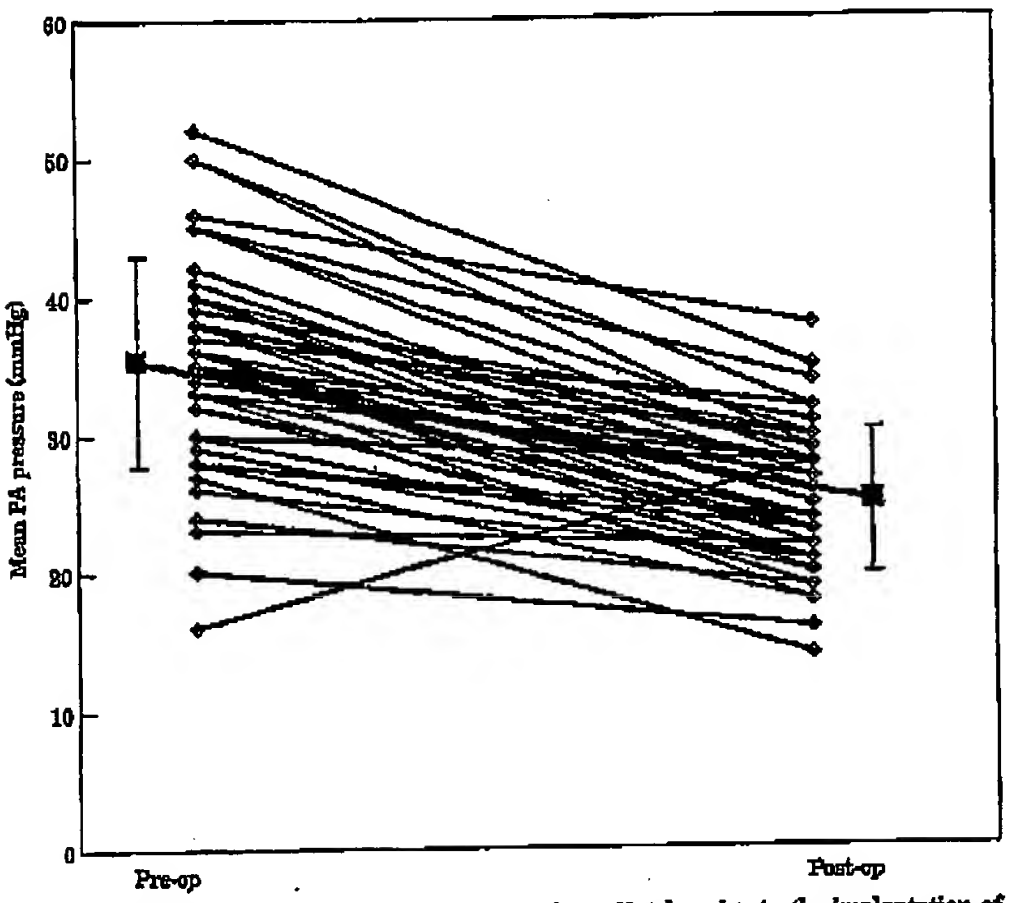

Figure 1 Mean pulmonary artery (PA) pressure immediately prior to the implantation of a ventricular support device and on return to the intensive care unit following the procedure.

pumping chamber is made of titanium and has a rough inner surface allowing for generation of an inner surface lining[13].

The average age of the patients was 45·3 years (range 15·0–67·4 years). At operation, all patients were in the intensive care unit requiring inotropic support. Pulmonary artery pressure fell immediately after the operation from a mean of 35·3 ± 1·1 mmHg to 25·1 ± 0·8 ($P<0·0001$) (Fig. 1). Mean systemic arterial pressure increased from 66·5 ± 1·2 at operation to 78·3 ± 1·3 at 1 week ($P<0·0001$). There was no difference between devices in the haemodynamic response ($P>0·2$).

The clinical outcomes are shown in Table 2. The mean duration of ventricular assist support was 124 days (range 3–796). Note that five subjects had sufficient recovery of ventricular function for their assist devices to be explanted, with long-term survival. These survivors all had a dilated cardiomyopathy, but had the same average age (45·0 ± 4·1 years), height (174 ± 4 cm) and cytokine levels as the main group. They had a higher cardiac index at implantation (2·1 l. min^{-1}. m^{-2}) than the main group, but ejection fraction and arterial pressures were the same. The survivors were heavier than the main group (85·2 ± 3·4 kg vs 75·2 ± 4·5; $P=0·2$). The survival for the group as a whole is shown in Fig. 2.

The results for cytokine assays for all patients are shown in Table 3 and Fig. 3. There were no differences between those who had a biventricular assist device implanted and those with a left ventricular assist. After device implantation, there was a significant initial fall in tumour necrosis factor α concentration, with a gradual return to pre-implantation values. In order to remove the bias induced by considering patients who died before the later stages of follow-up, we also show the data in Fig. 4 for those patients who survived with ventricular assist support for 90 days ($n=26$). There was no substantial difference between the two sets of results. There was no difference in the measured cytokines at the time of

Table 2 Patient outcomes

Outcome	n	Time to transplant/ left ventricular assist device removal/death (range)
Death	31	99 ± 86 (3–378)
Transplant	12	101 ± 80 (10–247)
Transplant then death	5	71 ± 21 (39–91)
Survival	5	350 ± 259 (180–769)

Times are displayed in days. For the group who died following transplantation, the individual survival data following transplantation were 1 day, 2 days, 4 days, 10 days and 675 days. For those who survived, the time to removal of assist device is shown.

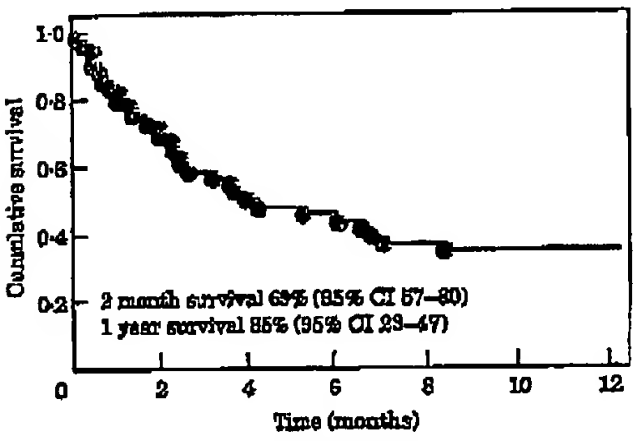

Figure 2 Kaplan–Meier survival curve showing times to first event. A first event is defined as death or transplantation. The data were censored at 1 year from assist device implantation.

operation between those who died during the first year of follow-up and those who survived (n=12). In Cox survival analyses, levels of the measured cytokines at operation did not predict outcome.

The rise in tumour necrosis factor α at 90 days follow-up was not associated with an increase in signs of infection. There was no rise in white cell count during this period (indeed, the white count fell slightly during follow-up; Table 3), and there was no correlation between the white cell count and tumour necrosis factor α at any time point. There was no interaction between the change in cytokine levels over time and clinical outcome (transplantation, death, survival).

There was no significant change in soluble tumour necrosis factor receptor type 1. There was a slight, but significant increase in soluble CD14 receptors over the time course of the study. Changes in elastase, interleukin-6 and C3a paralleled the changes in tumour necrosis factor α, although the decline in these variables continued to the 40 day time point before beginning to rise again.

There was a reduction in body mass after the operation (79·6 ± 2·6 kg pre-operatively; 73·2 ± 2·4 at 1 month (n=35; $P<0·001$; Fig. 5), and 72·5 ± 2·6 at 90 days). There was a similar reduction in body mass index from 24·9 ± 0·8 kg . m^{-2} pre-operatively to 23·3 ± 0·5 kg . m^{-2} at 1 month ($P<0·001$ vs baseline) and 23·0 ± 0·8 kg . m^{-2} at 90 days ($P>0·2$ for the comparison with 1 month). This difference was more marked when the mass of the devices was subtracted from the patients' weight (72·4 ± 14·3 kg at 1 month, 71·7 ± 14·3 at 90 days). There was no relation between body mass index and duration of heart failure (R=0·03; $P>0·5$).

Survival analysis

Those patients who survived 90 days following the operation (n=26) were heavier at the time of operation than those who died (83·1 (15·3) kg vs 73·4 (10·5); $P=0·008$). Pre-operative body mass index predicted survival as a continuous variable ($P=0·0053$). Figure 6 shows survival in patients with a body mass index above and below 25 kg . m^{-2}, which was the cut off for the group of patients in the highest tertile for body mass index.

Of the cytokines measured at baseline, only tumour necrosis factor receptor-1 weakly predicted survival ($P=0·02$). Urea also predicted outcome ($P=0·01$). There was no effect from electrolytes, blood count variables or liver function on survival. There was no effect from sex, age or underlying cause of heart failure on outcome. Only body mass index was an independent predictor of survival.

Table 3 Change in humoral variables from implantation of assist device in chronic heart failure patients

	Pre-op (n=46)	1 week (n=46)	40 days (n=35)	90 days (n=26)
TNFα (pg . ml^{-1})	9·66 ± 1·33	4·20 ± 1·00	6·59 ± 1·42	7·84 ± 1·45
sTNFR-1 (pg . ml^{-1})	3201 ± 238	3578 ± 352	2700 ± 368	3478 ± 477
sCD14 (μg . ml^{-1})	3·99 ± 0·15	4·30 ± 0·22	4·18 ± 0·22	5·02 ± 0·39
C3a (ng . ml^{-1})	1082 ± 45	812 ± 46	657 ± 51	713 ± 69
Elastase (μg . ml^{-1})	190·5 ± 14·3	90·2 ± 6·4	75·3 ± 7·6	77·9 ± 10·7
IL-6 (pg . ml^{-1})	131·3 ± 20·5	55·8 ± 17·3	21·8 ± 4·5	69·4 ± 45·0
C5a (ng . ml^{-1})	793 ± 161	992 ± 135	1130 ± 101	1106 ± 129
WCC (× 10^9 . l^{-1})	14·6 ± 0·8	14·8 ± 0·9	14·2 ± 1·4	11·4 ± 1·1
Hb (g . l^{-1})	106 ± 2	97 ± 2	97 ± 2	104 ± 3
Na^+ (mmol . l^{-1})	139·8 ± 0·7	138·4 ± 0·9	137·8 ± 0·8	137·5 ± 1·1
K^+ (mmol . l^{-1})	4·58 ± 0·07	4·44 ± 0·05	4·12 ± 0·07	4·20 ± 0·08
Urea (mmol . l^{-1})	29·7 ± 2·0	23·5 ± 2·4	18·3 ± 3·8	17·3 ± 2·5
Creatinine (μmol . l^{-1})	165·0 ± 9·0	114·9 ± 9·4	99·5 ± 8·2	121·1 ± 9·8

Differential white cell counts are not available. TNFα=tumour necrosis factor α; sTNFR-1=soluble tumour necrosis factor receptor type 1; sCD14=the soluble form of CD14; C3a and C5a=activated complement factors 3 and 5, respectively; IL-6=interleukin-6; WCC=white cell count; Hb=haemoglobin. The data are shown as means ± SEM.

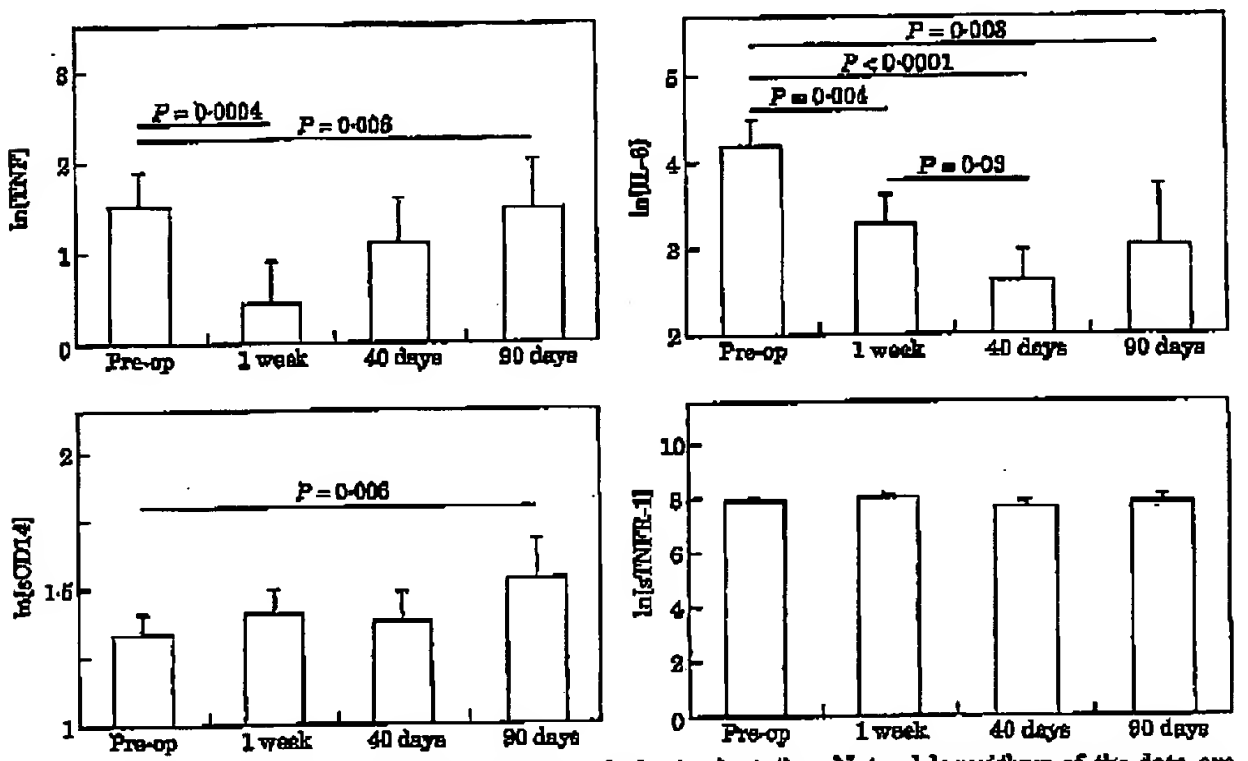

Figure 3 The behaviour of cytokine levels following device implantation. Natural logarithms of the data are shown as these were normally distributed. The error bars are the 95% confidence intervals.

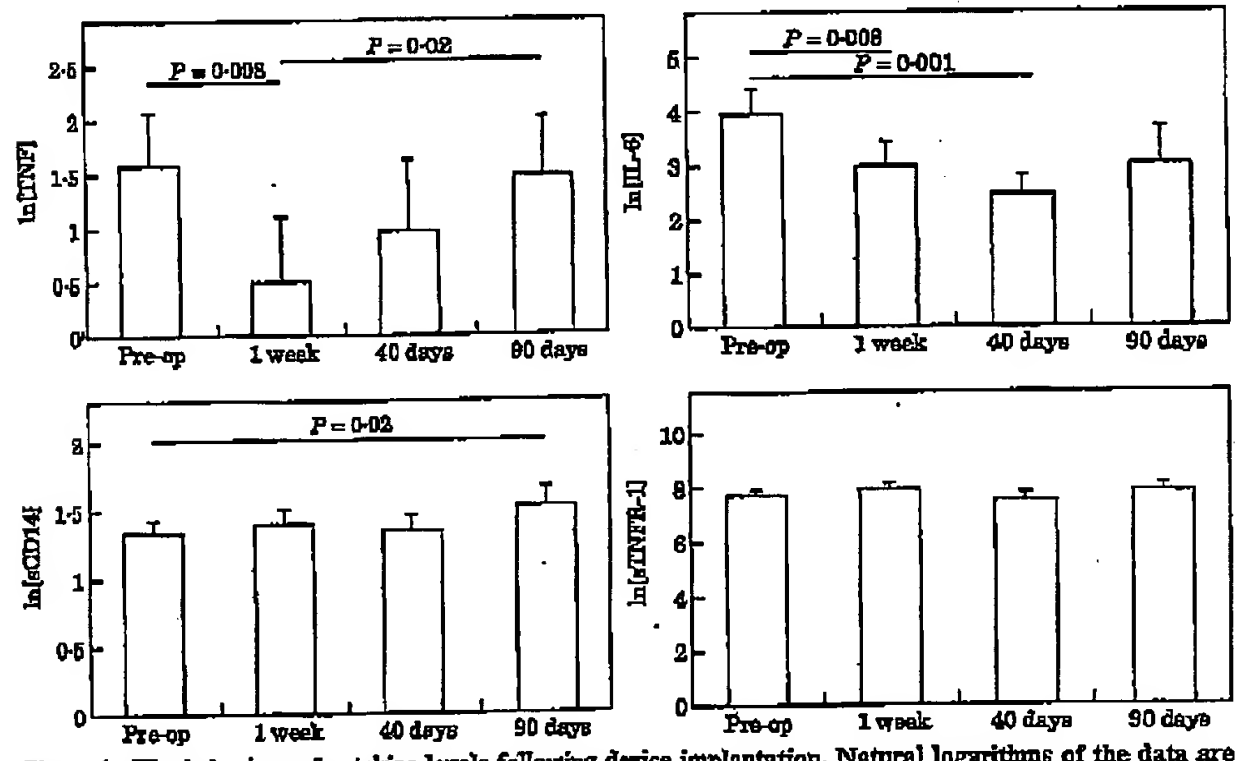

Figure 4 The behaviour of cytokine levels following device implantation. Natural logarithms of the data are shown as these were normally distributed. The error bars are the 95% confidence intervals. In this series of plots, data are shown only from those patients surviving until 90 days (n=26).

Correlation analysis

Correlations between variables are shown in Table 4. There was a close relationship between elastase and C3a (Fig. 7). At the time of operation, there were no correlations between haemodynamic variables and any of the inflammatory indices measured. There was a close

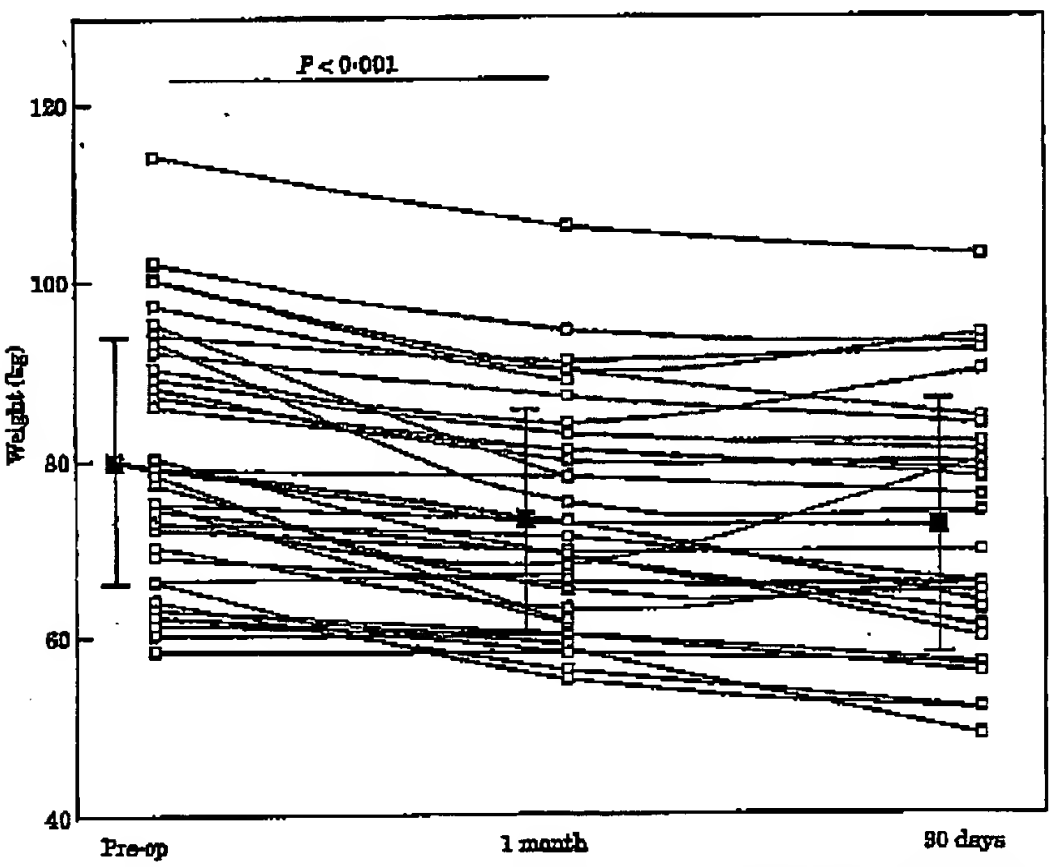

Figure 5 The pattern of weight loss in those patients surviving the first month of assist device implantation. The bolder lines represent two or more patients whose weight increased or decreased to the same level.

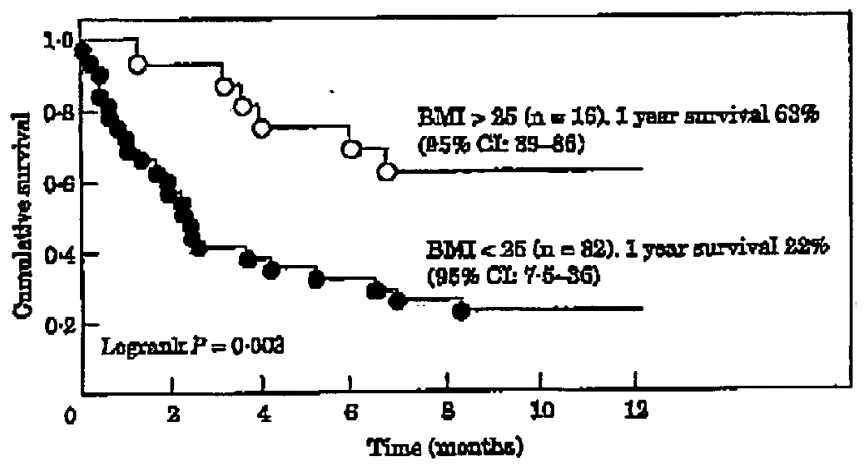

Figure 6 Survival in patients according to the body mass index (BMI) at time of assist device implantation.

relationship between urea and tumour necrosis factor receptor 1.

There was a very weak relationship between weight at operation and tumour necrosis factor receptor 1 ($r = -0{\cdot}34$; $P<0{\cdot}05$), and between weight and interleukin-6 ($r = -0{\cdot}37$; $P=0{\cdot}02$). There were no correlations between weight loss, expressed in absolute terms or as a proportion of initial weight, and change in cytokine level, expressed in absolute terms or as a proportion of initial level.

Discussion

We have studied cytokine responses to the implantation of a left ventricular assist device in patients with

Table 4 Univariate correlation matrix for the inflammatory mediators measured

	ln[TNFR-1]	ln[TNF]	ln[sCD14]	Ln[C3a]	ln[elastase]	ln[IL-6]	ln[C5a]	Urea
ln[TNF]	0·14							
ln[sCD14]	0·30	−0·11						
ln[C3a]	0·23	−0·03	0·06					
ln[elastase]	0·32	0·02	0·08	0·82 (<0·001)				
ln[IL-6]	0·35	−0·07	0·04	0·40 (<0·001)	0·40 (<0·001)			
ln[C5a]	0·32	−0·1	0·48 (<0·001)	0·02	0·12	−0·15		
Urea	0·63 (P<0·001)	0·26	0·25	0·12	0·16	0·17	−0·05	
WCC	0·003	0·22	0·21	0·33	0·35	0·006	−0·07	−0·05

Results are shown for data at the time of operation (n=48). TNFR-1=tumour necrosis factor receptor type 1; TNF=tumour necrosis factor; sCD14=soluble CD14; C3a and C5a=activated complement factors 3 and 5, respectively; IL-6=interleukin-6; WCC=white cell count.

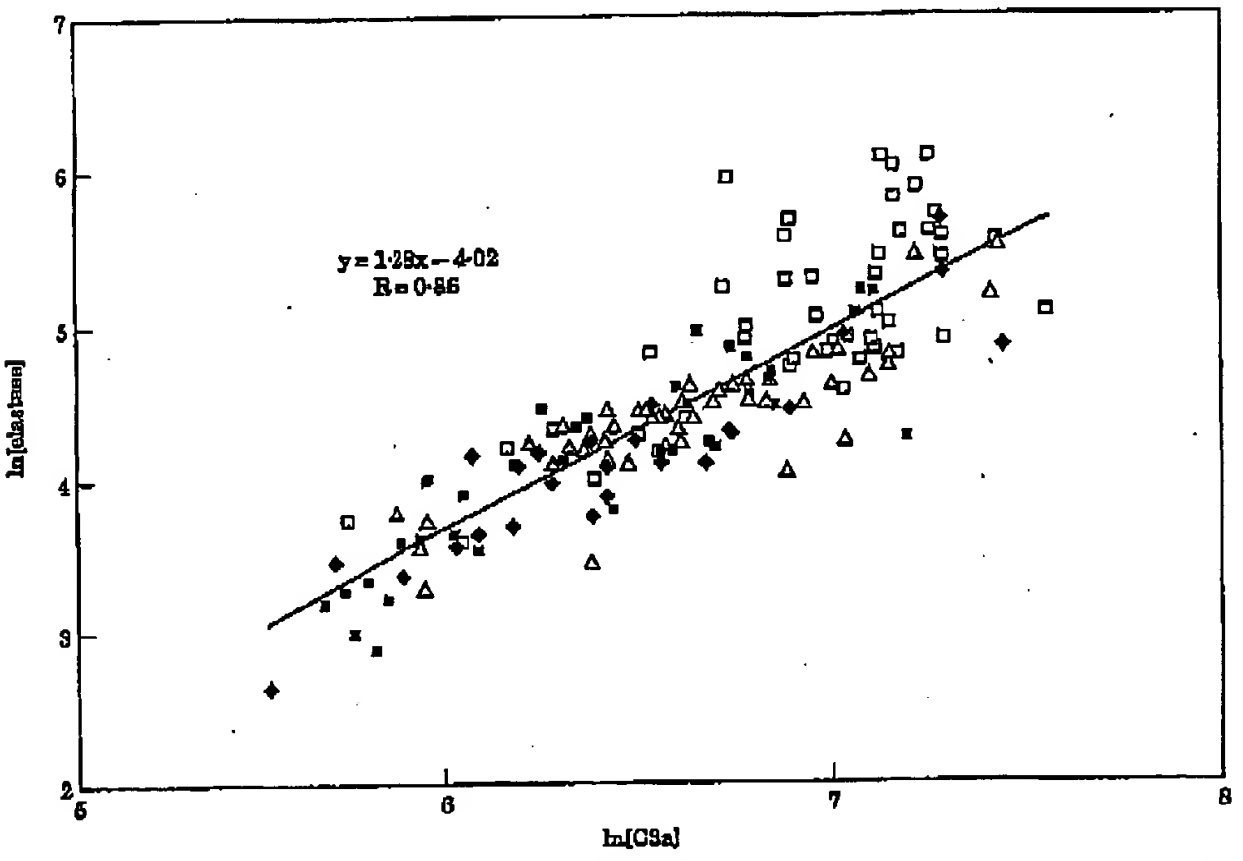

Figure 7 The relationship between elastase and activated C3. ■=before operation; △=1 week; ■=40 days; ◆=90 days.

end-stage heart failure. Device implantation results in a temporary fall in tumour necrosis factor α and interleukin-6, but these largely returned to pre-implantation levels by 90 days follow-up. Although none of the cytokines we measured independently predicted outcome, there was a strong relationship between body mass at the time of operation and clinical outcome.

Elevated levels of tumour necrosis α were first reported in 1990 by Levine *et al.* who studied heart failure patients with cachexia[1]. Many other immune cytokines have been reported to be elevated in chronic heart failure, such as interleukins 1[15], 2[15,16], 6[17] and 8[18], soluble tumour necrosis factor receptors[7,19], and leukocyte chemokines[20]. Associated with the immune activation is a generalized imbalance between anabolic and catabolic processes[2,21,22], such that catabolism predominates[23].

There are two complementary explanations for the origin of these phenomena. One asserts that abnormal

haemodynamics are the source of inflammatory and immune activation[4], and that chronic hypoxia may result in endothelial production of free radicals and consequently leukocyte activation[24]. The heart itself may be a source of immune activation by this hypothesis. A second asserts that immune activation is a consequence of exposure to exogenous antigen[7].

The clinical problem of end-stage heart failure can be tackled by heart transplantation, and increasingly by the implantation of ventricular assist devices, usually as a bridge to transplantation[25,26]. Problems with devices include thromboembolic events and possible systemic inflammatory responses related to blood contact with artificial surfaces[27]. We have previously shown that the degree of complement activation is a function of the severity of cardiogenic shock prior to circulatory support, rather than an effect of surface activation[28].

In the present study we sought to describe the pattern of inflammatory response to the implantation of a ventricular assist device. The device improves the haemodynamic deficit of severe chronic heart failure, but without removing the heart as a potential source of immune activation. In addition, it adds a potentially potent extra source of immune activation in the shape of an extensive foreign surface. However, if there is significant spillover from cardiac cytokine production, unloading the heart with an assist device should cause long-term reduction in peripheral cytokine levels in survivors.

Despite these potentially potent sources of additional inflammation, and the effects of major surgery, we have found an initial reduction in indices of inflammation as evidenced by a fall in levels of tumour necrosis factor α, interleukin-6 and activated complement. These observations accord with previous work that suggested that left ventricular assist device implantation reduces the expression of myocardial tumour necrosis factor α[29]. Assist device implantation can have a profoundly depressant effect on T-cell function lasting up to 3 months[30]. The fall in tumour necrosis factor α seen with mechanical assist is in contrast to what is seen with medical therapy for acute episodes of decompensation of chronic heart failure where levels do not fall quickly[7,31].

Why is there a gradual increase in indices of immune activation later during the course of the study? There is no sign that the patients are retaining fluid and becoming oedematous again. Equally, with the heart still supported by the assist device, it seems unlikely that the heart has started to secrete tumour necrosis factor α. It may be that there is low grade sepsis that we have not detected clinically, or it may reflect immunosuppression induced by surgery and illness, that is then subsequently wearing off. Inflammatory and immune activation may be independent of haemodynamic and functional changes.

We found no fall in the levels of CD14 and soluble tumour necrosis factor receptor; indeed there was a slight rise in CD14 over the period of the study. CD14 is thought to be representative of longer term exposure to endotoxin. The temporary fall in tumour necrosis factor α and interleukin-6 might be explained by a short-term reduction in ischaemia as a result of an increase in cardiac output. In the longer term, tumour necrosis factor α increases again (and other inflammatory markers never change) because the pathophysiological process resulting in inflammation is not altered by assist device implantation, as suggested by the persisting CD14 level.

We considered the possibility that changes in plasma volume might influence cytokine levels, but we saw no change in haemoglobin or haematocrit (which was influenced by surgical management). Therefore we believe that plasma volume could only have had a minor influence. Nevertheless, the volume of distribution of cytokines in heart failure patients is not known. In view of the loss of weight in the first week after surgery, this may have influenced results; future studies will have to address this issue in detail.

Cardiopulmonary bypass circuits have been shown to be potent stimulants of an inflammatory response in the short-term[32,33], but we saw a fall in activated complement and elastase at 1 week. This is perhaps surprising in view of the pro-thrombotic stimulus represented by the support device. It might be that the stress of illness and surgery resulted in suppression of the immune response[34]. Nevertheless, complement levels were higher than seen in normal subjects (C3a $<200\ ng.ml^{-1}$, C5a $<500\ ng.ml^{-1}$). Elastase was reduced to within the normal range ($<85\ \mu g.ml^{-1}$).

There is no currently available treatment specifically for increasing body weight in heart failure patients. Restoring cardiac output might have such an effect. We observed significant weight loss after the assist devices were implanted (6·5 kg, or 8·1% of body mass). This weight loss is probably due, at least in part, to reductions in body oedema, although we were not able specifically to test for this. It might be thought that greater pre-operative weight represents more fluid retention, and hence worse heart failure, but in this group of patients, a higher pre-operative weight conferred a better prognosis. This may reflect the known adverse effect of cachexia on prognosis[3]. The left ventricular assist device implantation did not seem to function as a specific anticachexia intervention, as suggested by the fact that there was a further (small) decline in body mass index by the 90 day follow-up.

Limitations

There is a possible confounder in the tumour necrosis factor α data in that the administration of heparin can enhance tumour necrosis factor production by monocytes[35]. All our patients were still receiving heparin at the 1 week time point, suggesting that the intrinsic fall in tumour necrosis factor α may be being under-estimated. Monocytes are the main site of tumour necrosis factor α production and we have not measured differential white cell counts, nor have we measured left ventricular volumes, and cannot thus assess any effect that change in wall stress may have on immune activation.

Conclusions

Patients undergoing ventricular assist device implantation for severe congestive heart failure as a bridge to transplantation have evidence of inflammatory activation as demonstrated by raised levels of tumour necrosis factor α and its receptor, activated complement and elastase and CD14. The levels of tumour necrosis factor α, interleukin-6, C3a and elastase are all reduced by device implantation, although levels start to rise again between 1 week and 1 month after operation. In the short-term in this group of severely diseased patients, left ventricular assist device implantation has no anti-cachectic effect. Lower body mass index at the time of device implantation is a powerful predictor of poor outcome.

References

[1] Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. N Engl J Med 1990; 323: 236–41.

[2] Anker SD, Chua TP *et al.* Hormonal changes and catabolic/anabolic imbalance in chronic heart failure: The importance for cardiac cachexia. Circulation 1997; 96: 526–34.

[3] Anker S, Ponikowski P, Varney S *et al.* Wasting as an independent risk factor for mortality in chronic heart failure. Lancet 1997; 349: 1050–3.

[4] Torre-Amione G, Kapadia S, Lee J *et al.* Tumor necrosis factor-α and tumor necrosis factor receptors in the failing human heart. Circulation 1996; 93: 704–11.

[5] Bryant D, Becker L, Richardson J *et al.* Cardiac failure in transgenic mice with myocardial expression of tumour necrosis factor-α. Circulation 1998; 97: 1375–81.

[6] Kubota T, McTiernan CF, Frye CS *et al.* Dilated cardiomyopathy in transgenic mice with cardiac-specific overexpression of tumour necrosis factor-α. Circ Res 1997; 81: 627–35.

[7] Anker SD, Egerer K, Volk H-D, Kox WJ, Poole-Wilson PA, Coats AJS. Elevated soluble CD14 receptors and and altert cytokines in chronic heart failure. Am J Cardiol 1997; 79: 1426–30.

[8] Niebauer J, Volk HD, Kemp M *et al.* Endotoxin and immune activation in chronic heart failure: a prospective cohort study. Lancet 1999; 353: 1838–42.

[9] Ziegler-Heitbrock, Ulevitch RJ. CD14: Cell surface receptor and differentiation marker. Immunol Today 1993; 14: 121–5.

[10] Shapiro SD. Elastolytic metalloproteinases produced by human mononuclear phagocytes. Potential roles in destructive lung disease. Am J Respir Crit Care Med 1994; 150: S160–4.

[11] Rosen GM, Pou S, Ramos CL, Cohen MS, Britigan BE. Free radicals and phagocytic cells. FASEB J 1995; 9: 200–9.

[12] McCarthy PM, Portner PM, Tobler HG, Starnes VA, Ramasamy N, Oyer PE. Clinical experience with the Novacor ventricular assist system. J Thorac Cardiovasc Surg 1991; 102: 578–87.

[13] Rose EA, Levin HR, Frazier HO, Burton NA, Lefrak EA. Artificial circulatory support with textured inner surfaces. Circulation 1994; 90 (Suppl): II87–91.

[14] Hetzer R, Hennig B, Schiessler A, Friedel N, Warnecke H, Adt M. Mechanical circulatory support and heart transplantation. J Heart Lung Transplant 1992; 11: 175–81.

[15] Blum A, Sclarovsky S, Rehavia E, Sholnt B. Levels of T lymphocyte subpopulations, interleukin 1 beta, and soluble interleukin 2 receptor in acute myocardial infarction. Am Heart J 1994; 127: 1226–30.

[16] Katz SD, Rao R, Berman JW *et al.* Pathophysiological correlates of increased serum tumor necrosis factor in patients with congestive heart failure. Relation to nitric oxide dependent vasodilation in the forearm circulation. Circulation 1994; 90: 12–6.

[17] Wiedermann CJ, Beimpold H, Herold M, Knapp E, Braunsteiner H. Increased levels of serum neopterin and decreased production of neutrophil superoxide anions in chronic heart failure with elevated levels of tumor necrosis factor alpha. J Am Coll Cardiol 1993; 22: 1897–901.

[18] Hasper D, Hummel M, Kleber FX, Reindl I, Volk HD. Systemic inflammation in patients with heart failure. Eur Heart J 1998; 19: 761–5.

[19] Ferrari R, Bachetti T, Confortini R *et al.* Tumour necrosis factor soluble receptors in patients with various degrees of congestive heart failure. Circulation 1995; 92: 1479–86.

[20] Aukrust P, Ueland T, Muller F *et al.* Elevated circulating levels of C-C chemokines in patients with congestive heart failure. Circulation 1998; 97: 1136–43.

[21] Anker SD, Clark AL, Kemp M *et al.* Tumour necrosis factor and steroid metabolism in chronic heart failure: possible relation to muscle wasting. J Am Coll Cardiol 1997; 30: 997–1001.

[22] Niebauer J, Pflaum C-D, Clark AL *et al.* Deficient insulin-like growth factor-I in chronic heart failure predicts altered body composition, anabolic deficiency, cytokine and neurohormonal activation. J Am Coll Cardiol 1998; 32: 393–7.

[23] Berry C, Clark AL. Catabolism in chronic heart failure. Eur Heart J 2000; 21: 521–32.

[24] Leyva F, Anker SD, Godsland IF *et al.* Uric acid in chronic heart failure: a marker of chronic inflammation. Eur Heart J 1998; 19: 1814–22.

[25] Loebe M, Hennig B, Müller J, Spiegelsberger S, Weng Y, Hetzer R. Long-term mechanical circulatory support as a bridge to transplantation, for recovery from cardiomyopathy, and for permanent replacement. Eur J Cardiothorac Surg 1997; 11 (Suppl): S18–24.

[26] Massad MG, McCarthy PM, Smedira NG *et al.* Does successful bridging with the implantable left ventricular device affect cardiac transplantation outcome? J Thorac Cardiovasc Surg 1996; 112: 1275–83.

[27] Kluft C, Doolejeward G, Emeis JJ. Role of the contact system in fibrinolysis. Semin Thromb Hemost 1987; 13: 50–68.

[28] Loebe M, Gorman K, Burger R, Gage JE, Harke C, Hetzer R. Complement activation in patients undergoing mechanical circulatory support. ASAIO J 1998; 44: M340–6.

[29] Torre-Amione G, Stetson SJ, Youker KA *et al.* Decreased expression of tumour necrosis factor-alpha in failing human myocardium after mechanical circulatory support: A potential mechanism for cardiac recovery. Circulation 1999; 100: 1189–93.

[30] Ankersmit HJ, Tugulea S, Spanier T *et al.* Activation-induced T-cell death and immune dysfunction after implantation of left-ventricular assist device. Lancet 1999; 354: 550–5.

[31] Vanderheyden M, Kerzschot E, Paulus WJ. Pro-inflammatory cytokines and endothelium-dependent vasodilation in the forearm. Serial assessment in patients with congestive heart failure. Eur Heart J 1998; 19: 747–52.

[32] Hammerschmidt DE, Stroneck DF, Bowers TK. Complement activation and neutropenia during cardiopulmonary bypass. J Thorac Cardiovasc Surg 1981; 81: 370–7.

[33] Butler J, Chong GL, Baigrie RJ. Cytokine response to cardiopulmonary bypass with membrane and bubble oxygenator. Ann Thorac Surg 1992; 53: 833–88.

[34] Keel M, Schregenberger N, Steckholzer U *et al.* Endotoxin tolerance after severe injury and its regulatory mechanisms. J Trauma 1996; 41: 430–7.

[35] Heinzelmann M, Miller M, Platz A, Gordon LE, Herzig DO, Polk. HC. Heparin and enoxaparin enhance endotoxin-induced tumour necrosis factor-alpha production in human monocytes. Ann Surg 1999; 229: 542–50.

Endotoxin and immune activation in chronic heart failure: a prospective cohort study

Josef Niebauer, Hans-Dieter Volk, Michael Kemp, Martin Dominguez, Ralf R Schumann, Mathias Rauchhaus, Philip A Poole-Wilson, Andrew J S Coats, Stefan D Anker

Summary

Background Immune activation in patients with chronic heart failure may be secondary to endotoxin (lipopolysaccharide) action. We investigated the hypothesis that altered gut permeability with bacterial translocation and endotoxaemia would be increased in patients with oedema secondary to congestive heart failure.

Methods We compared 20 patients who had chronic heart failure with recent-onset peripheral oedema (mean age 64 years [SD 10], New York Heart Association [NYHA] class 3·3 [0·7]), 20 stable non-oedematous patients with chronic heart failure (mean age 69 years [10], NYHA class 2·6 [0·7]), and 14 healthy volunteers (mean age 55 years [16]). Biochemical markers of endotoxaemia, inflammation, and immune activation were measured. Ten patients were studied within 1 week of complete resolution of oedema. Five patients survived longer than 6 months and were restudied again after remaining free of oedema for more than 3 months.

Findings Mean endotoxin concentrations were higher in oedematous patients with chronic heart failure than in stable patients with chronic heart failure (0·74 [SD 0·45] *vs* 0·37 EU/mL [0·23], p=0·0009) and controls (0·46 EU/mL [0·21], p=0·02). Oedematous patients had the highest concentrations of several cytokines. After short-term diuretic treatment, endotoxin concentrations decreased from 0·84 EU/mL [0·49] to 0·45 EU/mL [0·21], p<0·05) but cytokines remained raised. After freedom of oedema for more than 3 months after oedema resolved, endotoxin concentrations remained unchanged from the previous visit (0·49 EU/mL [0·06], p=0·45).

Interpretation Raised concentrations of endotoxin and cytokines are found in patients with chronic heart failure during acute oedematous exacerbation. Intensified diuretic treatment can normalise endotoxin concentrations. Our preliminary findings suggest that endotoxin may trigger immune activation in patients with chronic heart failure during oedematous episodes.

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Introduction

Some patients with chronic heart failure have features such as cardiac cachexia that may be due to activation of the immune system.[1,2] Increased expression of tumour necrosis factor α (TNFα) has been found in cardiac tissue of patients with chronic heart failure undergoing heart transplantation and the failing heart has been suggested as the cause of immune activation.[3] No link between a pathogenic process and cytokine activation has been documented in human beings with heart failure or in animal models. The cause of increased cytokine production in patients with heart failure remains unknown.

We have previously suggested that bacterial endotoxin, lipopolysaccharide, contributes to immune activation in chronic heart failure.[4] Acute venous congestion could lead to altered gut permeability for bacteria, endotoxin, or both, and to translocation of these materials into the circulation. In the circulation, lipopolysaccharide is bound by a serum protein, termed lipopolysaccharide-binding protein (LBP).[5] The lipopolysaccharide-LBP complex can interact with the CD14 membrane protein and Toll-like signalling receptors to start a signalling cascade that leads to increased cytokine production (figure 1). The extracellular domain of the CD14 receptor is shed after interaction and serum concentrations are thought to reflect the amount of endotoxin and cell interaction. The lipopolysaccharide-LBP ratio has been shown to be crucial for the immunostimulatory effects of lipopolysaccharide.[6] High concentrations of LBP, as seen during the acute-phase response, can completely block lipopolysaccharide effects *in vitro* and in a murine sepsis model.[7] Furthermore, patients with high concentrations of soluble CD14 (which shows endotoxin-cell interaction and shedding of CD14 from the cell membrane[8]) have strikingly increased concentrations of TNFα, soluble TNF receptor-I and receptor-2, and intracellular-adhesion molecule-1.[4]

The degree of bowel-wall oedema cannot be directly measured. The relation between central haemodynamics and the pathophysiological features of chronic heart failure is weak.[9] In animal models there is a poor relation between intracardiac pressures and intestinal perfusion.[10] We therefore separated patients according to the presence or absence of a reliable marker of acute venous congestion due to cardiac failure, namely peripheral oedema. Bowel-wall oedema that could cause altered gut permeability and bacterial (ie, endotoxin) translocation is most likely to occur with moderate to severe peripheral oedema.

Our main aim in this study was to measure endotoxin and cytokine concentrations in patients with chronic heart failure during an acute exacerbation with peripheral oedema and after short-term and long-term treatment with diuretics.

Methods

Participants

We studied prospectively 14 healthy volunteers (mean age 55 years [SD 16]) and 40 patients with chronic heart failure (mean age 68 years [15], p=0·11). We did the baseline studies between April and October, 1997. 20 stable patients were recruited during outpatient clinics on 3 specific days and 20 patients with moderate

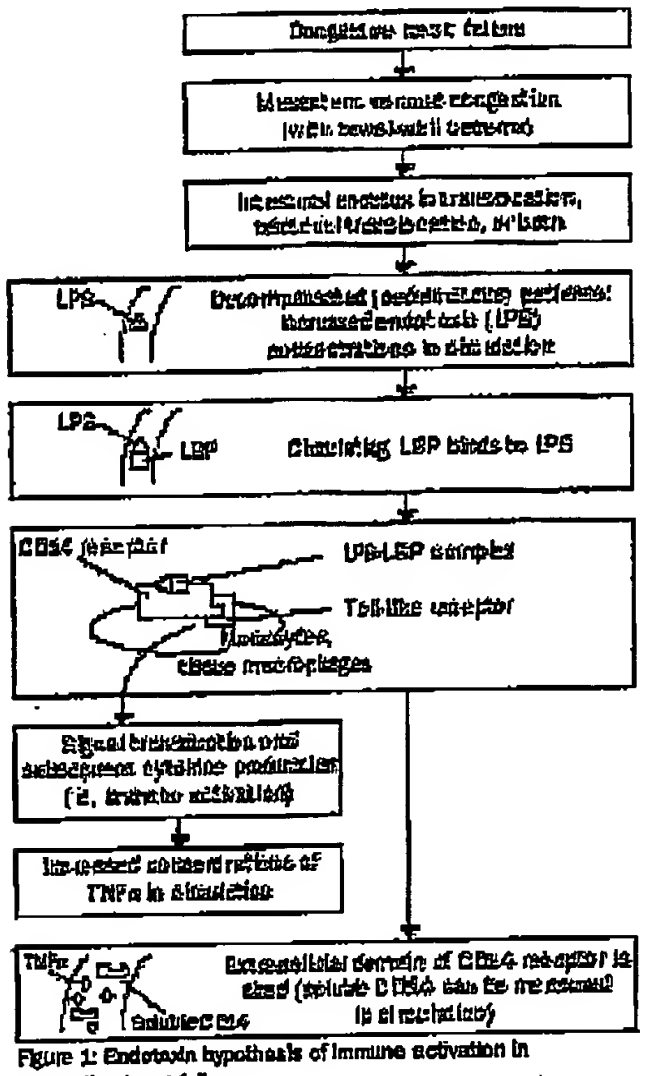

Figure 1: Endotoxin hypothesis of immune activation in congestive heart failure
LPS=lipopolysaccharide.

or severe oedema represented all decompensated patients at Royal Brompton Hospital, London, UK, during the time period, identified on attendance to the clinic or admission to the ward. Healthy volunteers were hospital staff and relatives of patients who agreed to participate. Only one healthy person declined participation. We excluded data from three volunteers aged younger than 35 years to achieve a similar mean age in all groups. The causes of chronic heart failure were ischaemic in 27 patients and idiopathic dilated cardiomyopathy in 13 patients. The diagnosis of chronic heart failure was based on symptoms arising during exercise, cardiomegaly, and documented left-ventricular dysfunction (all patients had a left-ventricular ejection fraction measured by echocardiography or radionuclide ventriculography of <40%). No patient or volunteer had clinical signs of infection, rheumatoid arthritis, or cancer.

Patients were treated with diuretics (n=38), angiotensin-converting-enzyme inhibitor (n=36), digoxin (n=14), aspirin (n=17), amiodarone (n=16), and nitrates (n=15) in various combinations. We did extended follow-up of ten oedematous patients who lived close to our hospital (five New York Heart Association [NYHA] class IV, five class III) after treatment with increased doses of diuretics (increase of furosemide up to 120 mg/day, with addition of bendroflumethiazide 2·5 mg or 5·0 mg once daily, metolazone 5 mg or 10 mg once daily, or both). Of these patients, three had to be admitted for 3–8 days for intravenous diuretic treatment.

After a median of 14 days (range 7–89) we restudied these patients within 1 week of complete resolution of oedema (after treatment six NYHA class III, four class II; mean weight loss 3·6 kg [0·9, range 2·5–5·0]). Five patients regained clinical stability (one NYHA class III, four class II) and were restudied again 14–92 weeks (mean 21 weeks [7]) after the initial investigation when they had been free of peripheral oedema for more than 3 months. The remaining five patients did not attain a stable clinical state and died 2–8 months after the initial investigation without having been restudied. The research protocol was approved by the ethics committee of the Royal Brompton Hospital, and all patients and volunteers gave written informed consent.

Assays

Blood samples were collected after rest for at least 15 min. A polyethylene catheter was inserted into an antecubital vein and 8 mL of blood were drawn into endotoxin-free tubes (Endo Tube ET, Chromogenix AB, Sweden). 30 mL samples were also taken for biochemical and cytokine measurements. After immediate centrifugation, blood and plasma samples were stored at −80°C until analysis. In addition, 5 mL blood was taken into tubes containing edetic acid for fluorescence-activated cell-sorting analysis.

Concentrations of endotoxin were measured with a commercially available kit (Limulus Amebocyte Lysate QCL-1000 test kit, BioWhittaker Inc, Walkersville, USA). The normal concentration of endotoxin in this assay in healthy people is <0·50 EU/mL. The within-assay coefficients of variation at concentrations of 0·35 EU/mL and 0·82 EU/mL were 9·9% and 9·6%; between-assay coefficients of variation were 16·6% and 13·3%, respectively. For repeated blood samples in non-oedematous patients the coefficient of variation was 10·8%. The lower limit of detection was 0·03 EU/mL.

LBP was measured by ELISA.[11] Total TNFα was measured with an ELISA kit (Medgenix, Fleurus, Belgium; sensitivity 9·0 pg/mL; test not influenced by soluble TNF receptors). ELISA kits (R&D Systems, Minneapolis, MN, USA) were used to measure soluble TNF receptor-1 and receptor-2, and interleukin 6; lower limits of detection of the assays were 25 pg/mL, 2 pg/mL, and 0·0094 pg/mL, respectively. Soluble CD14 was assessed by ELISA (IBL, Hamburg, Germany). Plasma procalcitonin concentrations were measured by an immunoluminometric assay (BRAHMS, Berlin, Germany).[12]

In a subgroup of ten non-oedematous and seven oedematous patients, as well as in all healthy volunteers, whole-blood samples were taken in potassium edetic-acid tubes (Vacutainer Systems, Falcon BD, Oxford, UK) and stained with fluorescently labelled monoclonal antibodies (Coulter Electronics, Luton, UK) to

	Healthy volunteers (n=34)	CHF no oedema (n=20)	CHF oedema (n=20)
Demography (mean [SD])			
Age (years)	58 (18)	63 (13)	64 (10)
Weight (kg)	74 (7)	76 (8)	78 (9)
NYHA class	..	2·5 (0·7)	3·3 (0·6)*
Cause			
Ischaemic	..	16	11
Idiopathic dilated	..	4	9
Clinical (mean [SD])			
Sodium (mmol/L)	139 (1·5)	137 (4·6)	134 (4·6)†
Creatinine (μmol/L)	82 (15)	131 (56)	219 (160)‡§
Urea (mmol/L)	5·4 (0·9)	11·0 (7·6)	20·0 (12·6)‡‖
Uric acid (mmol/L)	308 (83)	417 (146)¶	640 (174)*‡
Aspartate aminotransferase (U/L)	28 (14)	24 (5)	23 (8)
Alanine aminotransferase (U/L)	23 (10)	17 (4)¶	14 (4)‖
Lymphocyte profile (mean [SD])			
CD4	47 (8)	51 (11)	35 (15)‖¶
CD8	22 (7)	25 (14)	28 (20)
CD4/8 ratio	2·5 (1·2)	2·3 (2·4)	2·6 (2·6)
cp4/25 ratio	6·7 (4·2)	5·5 (2·4)	10·6 (8·7)
CD8/25 ratio	4·7 (2·4)	8·7 (4·9)	11·6 (10·7)‖

CHF=chronic heart failure.
*p<0·001 vs CHF no oedema. †p<0·01 vs healthy volunteers. ‡p<0·001 vs healthy volunteers. §p<0·05 vs CHF no oedema. ‖p<0·05 vs healthy volunteers. ¶p<0·01 vs CHF no oedema.

Table 1: Characteristics of patients with chronic heart failure with and without peripheral oedema and healthy volunteers

	Healthy volunteers (n=24)	CHF no oedema (n=20)	CHF oedema (n=20)
Endotoxin (EU/mL)	0·46 (0·21)	0·37 (0·23)	0·74 (0·45)*†
LBP (µg/mL)	9·6 (4·0)	10·4 (5·3)	12·1 (6·0)
Lipopolysaccharide/log LBP ratio	0·54 (0·20)	0·44 (0·30)	0·75 (0·49)‡
TNFα (pg/mL)	24·8 (8·9)	25·8 (7·8)	36·6 (12·6)‡§
Soluble TNF receptor-1 (pg/mL)	708 (213)	1077 (529)	1822 (1339)‡‖
Soluble TNF receptor-2 (pg/mL)	1465 (535)	2096 (1350)	3143 (1690)§¶
Soluble CD14 (ng/mL)	3456 (583)	3574 (454)	4249 (685)‡‖
Procalcitonin (ng/mL)	87 (36)	106 (72)	145 (94)
Interleukin-6 (pg/mL)	2·0 (0·4)	4·8 (5·5)	14·7 (17·3)‡§
C-reactive protein (mg/L)	5·8 (1·7)	9·6 (9·5)	15·7 (17·1)§¶

*p<0·05 vs healthy volunteers. †p<0·001 vs CHF no oedema. ‡p<0·01 vs CHF no oedema. §p<0·01 vs healthy volunteers. ‖p<0·001 vs healthy volunteers. ¶p<0·05 vs CHF no oedema.

Table 2: Mean (SD) plasma concentrations of endotoxin and inflammatory markers in healthy volunteers and patients with chronic heart failure

determine peripheral lymphocyte phenotype and the proportion of CD25 receptor-positive T cells. A staining excess of antibody, determined by titration (data not shown), was placed into 12×75 mm polypropylene tubes (Rikay, Hampshire, UK). Two tubes were analysed for each patient's sample. The first tube contained control monoclonal mouse antihuman antibodies isotypically matched to the test antibodies in the second tube. The antibody-fluorochrome conjugates used were CD3-PC5, CD4-FITC, CD8-ECD, and CD25R-RD1. The formic-acid lysed whole-blood protocol was used in the multi-Q-prep (Coulter Electronics, Luton, UK). Lymphocyte gating was set on forward compared with side-scatter dot plot, and compensation was established by the combining of single-colour-stained leucocyte populations. Four-colour flow cytometry was done on the Coulter XL-MCL with System II software (version 2.0).

Statistical analysis

We assessed normality of distribution with the Kolmogorov-Smirnov test. Unpaired Student's *t* test, paired *t* test, ANOVA with Fisher's post-hoc test (with allowance for multiple testing), and the Mann-Whitney *U* test were used where appropriate. Data are presented as mean (SD). We also used univariate-correlation and multivariate-correlation analyses to establish the relation between variables. We took $p<0·05$ to be significant.

Results

In tables 1 and 2, baseline clinical characteristics and results of immunological and humoral measurements are shown. Endotoxin concentrations were highest in heart-failure patients with peripheral oedema, compared with heart-failure patients without oedema (98%) and controls (59%, p=0·0027; figure 2). Plasma concentrations of LBP did not differ between groups, but there was a raised lipopolysaccharide/log LBP ratio in the heart-failure patients with oedema compared with those without oedema (71%, p<0·01). In oedematous heart-failure patients, plasma concentrations were significantly higher for C-reactive protein, TNFα, soluble TNF receptor-1 and receptor-2, interleukin-6, and soluble CD14 (table 2) than for all other groups.

Among all participants (n=54), concentrations of soluble CD14 correlated significantly with endotoxin ($r=0·30$, $p<0·05$). This correlation was not significant when patients or healthy volunteers were analysed separately. In all patients with chronic heart failure, soluble CD14 correlated with TNFα ($r=0·32$, $p<0·05$) and soluble TNF receptor-1 ($r=0·45$, $p<0·01$). There was a correlation between soluble CD14 and soluble TNF receptor-2 in patients with stable chronic heart failure ($r=0·61$, $p<0·01$).

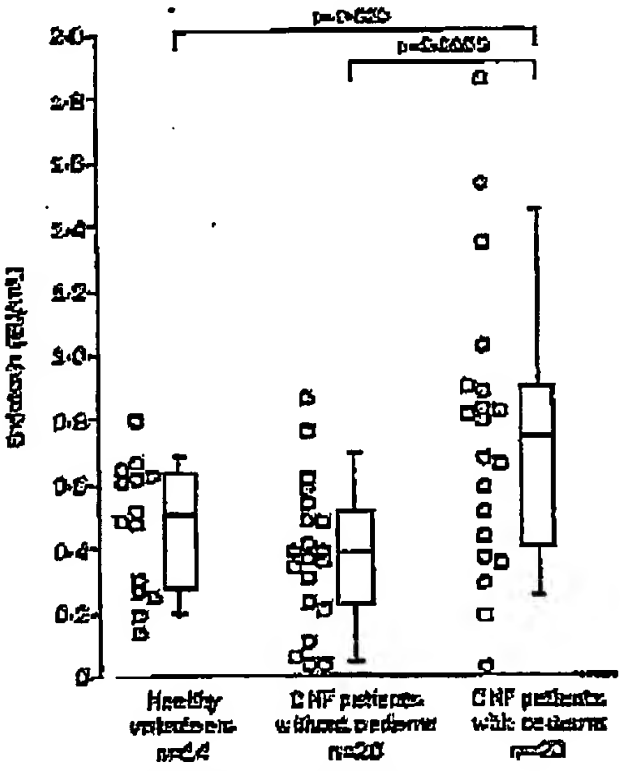

Figure 2: Plasma endotoxin concentration in healthy volunteers and heart-failure patients with and without oedema
Short horizontal lines=10th and 90th percentiles; long horizontal lines=25th, 50th, and 75th percentiles.

No simple correlations existed between creatinine or urea plasma concentrations and lipopolysaccharides at baseline, nor between changes in markers of kidney function over time compared with changes of lipopolysaccharide or cytokine concentrations over time (data not shown). Therefore, a bias because of latent abnormalities of kidney function seen in some oedematous patients is unlikely.

Intensive diuretic treatment for a mean of 23 days (8) in ten patients with chronic heart failure resulted in a mean weight decrease of 3·6 kg (range 2·5–5·0), and improvement in the functional NYHA class in nine of the ten patients. In eight of these, endotoxin plasma concentration was decreased from 0·96 EU/mL (0·47) to 0·45 EU/mL (0·24). In two patients with normal concentrations of endotoxin at baseline, concentrations after diuretic treatment were 9% and 36% higher than at baseline, but still in the normal range (<0·5 EU/mL). In all ten patients the lipopolysaccharide concentrations fell from 0·84 EU/mL (0·49) to 0·45 EU/mL (0·21, p=0·049;

	Baseline (n=10)	After diuretic treatment (n=10)	p
Endotoxin (EU/mL)	0·84 (0·49)	0·45 (0·21)	<0·05
LBP (µg/mL)	10·2 (3·7)	12·7 (7·5)	0·27
Lipopolysaccharide/log LBP ratio	0·85 (0·44)	0·23 (0·57)	0·033
TNFα (pg/mL)	39·9 (13·2)	40·2 (12·0)	0·82
Soluble TNF receptor-1 (pg/mL)	2356 (1214)	2765 (1291)	0·09
Soluble TNF receptor-2 (pg/mL)	3751 (1185)	4029 (1497)	0·46
Soluble CD14 (ng/mL)	4474 (537)	4490 (764)	0·99
Procalcitonin (ng/mL)	159 (82)	219 (104)	0·17
Interleukin-6 (pg/mL)	19·4 (22·0)	18·3 (25·9)	0·60
C-reactive protein (mg/L)	15·6 (11·0)	20·0 (20·7)	0·00

Table 3: Mean (SD) plasma concentrations of endotoxin and inflammatory markers in oedematous patients before and after diuretic treatment

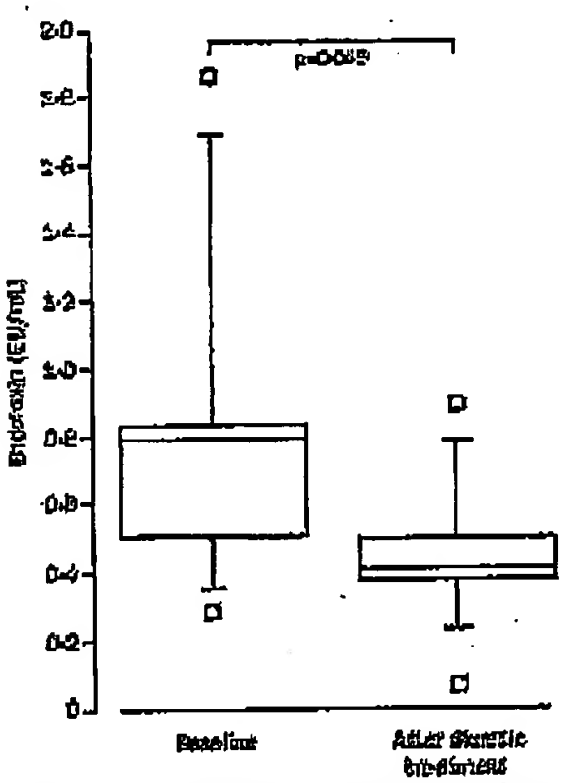

Figure 3: Effect of intensified diuretic treatment on plasma endotoxin concentrations in ten patients with chronic heart failure who had peripheral oedema

Short horizontal lines=10th and 90th percentiles; long horizontal lines=25th, 50th, and 75th percentiles; o=deviates value outside 10th and 90th percentiles.

figure 3). The effect of diuretic treatment on the endotoxin and inflammatory markers are shown in table 3. During extended follow-up, five patients were restudied when free of oedema for more than 3 months after 21 weeks (7). Endotoxin concentrations at the third visit did not differ from those at the second visit after a mean of 19 days (0·39 [0·22] *vs* 0·49 EU/mL [0·06], p=0·45), but TNFα concentrations were lower (39·6 [12·4] *vs* 31·0 pg/mL [5·7], p=0·079)

Discussion

We have shown that endotoxin concentrations and proinflammatory cytokines are raised in patients with heart failure who have peripheral oedema. Raised endotoxin concentrations were normalised by lengthened diuretic treatment. The endotoxaemia in these patients was not associated with a strong acute-phase response that would have led to an increased hepatic LBP synthesis and subsequent blocking of lipopolysaccharide effects. These results lend credence to the hypothesis that bacterial endotoxin may be an important stimulus of immune activation in patients with chronic heart failure. This finding may open various options for treatment of patients with chronic heart failure that could be directed against bacteria in the bowel, the translocation process, and endotoxin itself, the binding sites of bacterial endotoxin on immune competent cells, or both.

The complex of endotoxin and endotoxin-binding protein activates monocytes and tissue macrophages via the CD14 and Toll-like receptor proteins,[12] which stimulates the production of TNFα and other cytokines (figure 1). Previous studies suggested that increased soluble CD14 concentrations might be related to endotoxaemia.[4] We established that oedematous patients have the highest concentrations of soluble CD14 and lipopolysaccharide, but in homogeneous groups of patients there was no direct numeric relation between the two variables. Shed, and therefore soluble, CD14 receptors are thought to reflect the amount of endotoxin/cell interaction in the long term. By contrast, endotoxin has a short plasma half-life (10–30 min), which may explain why soluble CD14 concentrations are more closely related to cytokine than endotoxin concentrations.[4]

The concentrations of endotoxin in our study were well below those seen in septic shock.[14] Patients with chronic heart failure had no signs of active infection, and the moderate increases in plasma endotoxin are in keeping with the hypothesis of a translocation process. Possibly, it is endotoxin itself rather than bacteria that translocates. Lipopolysaccharides at baseline did not correlate significantly with renal function (as estimated by creatinine and urea) although this finding cannot completely exclude an influence of renal function on cytokine clearance.

Although intensified diuretic therapy resulted in normalisation of endotoxin concentrations, treatment did not lead immediately to lowered cytokine plasma concentrations, which is in keeping with a previous study.[15] This effect may be due to a concentration effect, resulting from the loss of up to 5 kg body water or long-term activation of monocytes or macrophages after brief exposure to an endotoxin stimulus during a phase of clinical deterioration with increased venous congestion. Alternatively, the lack of cytokine decrease immediately after clinical improvement may be due to a change in monocyte or macrophage lipopolysaccharide sensitivity (ie, "normalised" endotoxin concentrations may still cause increased cytokine production). Indeed, such an increased cellular sensitivity to lipopolysaccharides has been documented in patients with chronic heart failure who had acute decompensation.[16] The previously documented raised TNFα concentrations in cardiac tissue of patients with endstage chronic heart failure may also be due to cardiomyocytes or tissue monocytes releasing increased amounts of cytokines upon stimulation by lipopolysaccharides because of decompensation or hypersensitive cardiomyocytes. In cardiomyocytes of heart transplantation recipients (especially in patients with ischaemic chronic heart failure) increased baseline and lipopolysaccharide-stimulated TNFα production has been reported.[17] In our study, after a long phase of clinical stability, TNFα plasma concentrations showed a strong trend to decrease back to normal, and, therefore, the process of normalisation of cytokine secretion seems to be slow.

Tolerance of monocytes or macrophages to endotoxin can be induced in vivo and in vitro by endotoxin itself. Such an effect frequently occurs after severe injury.[18] One important mediator of lipopolysaccharides hyposensitivity is interleukin-10.[19] Compared with controls, we found interleukin-10 to be lower in stable patients with chronic heart failure.[4] Increased cardiac-wall stress and general tissue hypoxia (both via local free-radical generation and subsequent stimulation of the nuclear factor-κ B pathway) and hormonal catabolic and anabolic imbalance (especially in patients with muscle wasting[20]) may lead to immunological hypersensitivity. Endotoxin may, therefore, be an important stimulus for cytokine production in the heart and in the periphery even in the absence of oedema. In-vitro low concentrations of lipopolysaccharides have

detrimental effects on cardiomyocytes. These effects are indirect through the release of other substances,[25] but direct effects also have been seen.[26] In vivo there may be a dynamic balance between heart function and immune activation in patients with chronic heart failure, and over time patients with frequent oedematous episodes may deteriorate because of the cardiodepressant and metabolic consequences of raised TNFα concentrations. Better control of oedema in chronic heart failure may therefore, be beneficial.

In stable ambulatory patients with chronic heart failure, a significant excess concentration of cytokines from the heart could not be shown,[27] which suggests that cardiac production may not be the main source of the raised peripheral cytokine plasma concentrations. In support of the importance of peripheral hypoxia, measures of increased oxidative stress have been found to correlate with soluble TNF receptor-1 and receptor-2 concentrations.[28] We have shown that peak leg blood flow after ischaemia in clinically stable patients with chronic heart failure is inversely related to TNFα plasma concentrations. This effect may be due to a relation between hypoxia and TNFα production or toxic effects of TNFα on endothelial function.[29] Hypoxia may not be the most important cytokine trigger in chronic heart failure because of the cytokine profile. Raised interleukin-6 plasma concentrations can be attributed to peripheral hypoxic conditions,[30] which will occur in chronic heart failure, but there is no report that hypoxia leads to raised concentrations of TNFα, procalcitonin, or soluble TNF receptor-1 or receptor-2. Soluble CD14 receptors are, by contrast, characteristic of endotoxin action, but not of hypoxic disorders.[31]

This study shows the presence of raised plasma endotoxin concentrations in patients with chronic heart failure and peripheral oedema. In the presence of unchanged concentrations of endotoxin binding protein, the raised endotoxin concentration reflects a potentially pathogenic situation that leads to cytokine induction. We show that normalisation of endotoxin concentrations can be achieved by intensified diuretic treatment. Bacterial endotoxin may be an important stimulus of immune activation in patients with chronic heart failure. Our studies are preliminary and further investigations are needed. Nevertheless, these findings may open various new options for treatment directed against bacteria in the bowel, the translocation process, and endotoxin itself, the binding sites of bacterial endotoxin on immune competent cells, or both.

Contributors

Stefan Anker and Andrew Coats developed the endotoxin hypothesis and with Philip Poole-Wilson designed the study. Josef Niebauer and Stefan Anker coordinated the study. Josef Niebauer did all clinical assessments with the help of Mathias Rauchhaus. Michal Kemp measured endotoxin and TNFα. Mercin Dandinguez did all lymphocyte analyses. Hans-Dieter Volk and Ralf Schumann advised on immunological issues and measured all other cytokines and LBP. Josef Niebauer and Stefan Anker analysed the data and prepared the manuscript with the help of Philip Poole-Wilson and Andrew Coats. Hans-Dieter Volk and Ralf Schumann edited the manuscript.

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References

1 Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. *N Engl J Med* 1990; 323: 236–41.
2 Anker SD, Swan JW, Clua TP, et al. Hormonal changes and catabolic/anabolic imbalance in chronic heart failure: the importance of cardiac cachexia. *Circulation* 1997; 96: 526–34.
3 Torre-Amione G, Kapadia S, Lee J, et al. Tumor necrosis factor-α and tumor necrosis factor receptors in the failing human heart. *Circulation* 1996; 93: 704–11.
4 Anker SD, Egerer K, Volk H-D, Kox WJ, Poole-Wilson PA, Coats AJS. Elevated soluble CD14 receptors and altered cytokines in chronic heart failure. *Am J Cardiol* 1997; 79: 1426–30.
5 Schumann RR, Leong SR, Flaggs GW, et al. Structure and function of lipopolysaccharide binding protein. *Science* 1990; 249: 429–31.
6 Tobias PS, Soldau K, Ivanie NM, Eichbach P, Weiss P. Lipopolysaccharide (LPS) binding proteins BPI and LBP form different types of complexes with LPS. *J Biol Chem* 1997; 272: 18682–85.
7 Lamping N, Dettmer R, Schröder NWJ, et al. LPS-binding protein protects mice from septic shock caused by LPS or gram-negative bacteria. *J Clin Invest* 1998; 101: 2065–71.
8 Ziegler-Heitbrock, Ulevitch RJ. CD14: cell surface receptor and differentiation marker. *Immunol Today* 1993; 14: 121–25.
9 Clark AL, Poole-Wilson PA, Coats AJ. Exercise limitation in chronic heart failure: central role of the periphery. *J Am Coll Cardiol* 1996; 28: 1092–102.
10 Sommer T, Wessely C, Hegler M, et al. Early effects of catecholamine therapy on mucosal integrity, intestinal blood flow, and oxygen metabolism in porcine endotoxin shock. *Ann Surg* 1998; 228: 299–48.
11 Lamping N, Hoess A, Yu B, et al. Effect of site-directed mutagenesis of basic residues (Arg 94, Lys 95, Lys 99) of lipopolysaccharide (LPS)-binding protein on binding and transfer of LPS and subsequent immune cell activation. *J Immunol* 1996; 157: 4648–56.
12 Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. *Lancet* 1993; 341: 515–18.
13 Yang RB, Mark MR, Gray A, et al. Toll-like receptor-2 mediates lipopolysaccharide-induced cellular signalling. *Nature* 1998; 395: 284–88.
14 Gomez-Jimenez J, Salgado A, Mourelle M, et al. L-arginine: nitric oxide pathway in endotoxemia and human septic shock. *Crit Care Med* 1995; 23: 259–58.
15 Vandenheyden M, Knaapbot E, Paulus WJ. Pro-inflammatory cytokines and endothelium-dependent vasodilation in the forearm: serial assessment in patients with congestive heart failure. *Eur Heart J* 1998; 19: 747–52.
16 Vochaf S, Brost B, Stille-Siegener M, Grumbach IM, Kremer H, Figulla HR. Monocyte activation in congestive heart failure due to coronary artery disease and idiopathic dilated cardiomyopathy. *Int J Cardiol* 1998; 63: 237–44.
17 Wagner DR, McTiernan C, Sanders VJ, Feldman AM. Adenosine inhibits lipopolysaccharide-induced secretion of tumor necrosis factor-alpha in the failing human heart. *Circulation* 1998; 97: 521–24.
18 Keel M, Schregenberger N, Steckholzer U, et al. Endotoxin tolerance after severe injury and its regulatory mechanisms. *J Trauma* 1996; 41: 430–37.
19 Rassow F, Syrbe U, Meisel C, et al. Mechanism of endotoxin desensitization: involvement of interleukin 10 and transforming growth factor beta. *J Exp Med* 1995; 181: 1887–92.
20 Anker SD, Clark AL, Kemp M, et al. Tumor necrosis factor and steroid metabolism in chronic heart failure: possible relation to muscle wasting. *J Am Coll Cardiol* 1997; 30: 997–1001.
21 Lew WY, Ryan J, Yasuda S. Lipopolysaccharide induces cell shrinkage in rabbit ventricular cardiac myocytes. *Am J Physiol* 1997; 272: H2989–93.
22 Starr RG, Lader AS, Phillips GC, Stroman CR, Abel FL. Direct action of endotoxin on cardiac muscle. *Shock* 1995; 3: 380–84.
23 Munger MA, Johson B, Amber IJ, Callahan KS, Gilbert EM. Circulating concentrations of proinflammatory cytokines in mild or moderate heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1996; 77: 723–27.
24 Keith M, Geranmayegan A, Sole MJ, et al. Increased oxidative stress in patients with congestive heart failure. *J Am Coll Cardiol* 1998; 31: 1352–56.
25 Anker SD, Volterrani M, Egerer KR, et al. Tumor necrosis factor alpha as a predictor of peaking blood flow in patients with chronic heart failure. *Q J Med* 1998; 91: 199–203.
26 Yan SF, Tritto I, Pinsky D, et al. Induction of interleukin-6 (IL-6) by hypoxia in vascular cells. *J Biol Chem* 1995; 270: 11463–71.
27 Eggesbo JB, Hjermann I, Lund PK, Joo GB, Ovstebo R, Kierulf P. LPS-induced release of IL-1 beta, IL-6, IL-8, TNF-alpha and sCD14 in whole blood and PBMC from persons with high or low levels of HDL-lipoprotein. *Cytokine* 1994; 6: 521–29.

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Comprehensive guidelines for the diagnosis and treatment of chronic heart failure
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1. Diagnosis of chronic heart failure

1.1. Introduction and methodology

The aim of this report is to provide practical guidelines for the diagnosis, assessment and treatment of heart failure for use in clinical practice and in addition for epidemiological surveys and for clinical trials. The recommendations in these guidelines should always be considered in the light of local regulatory requirements for the administration of any chosen drug or device. This report is a comprehensive summary of the full report [1]. The full report should be used when in doubt or when further information is required.

1.1.1. Level of evidence

Recommendations regarding treatments have been based on the degree of available evidence.

Level of evidence	Available evidence
A	At least two randomised trials supporting recommendation
B	One randomised trial and/or meta-analysis supporting recommendation
C	Consensus statement from experts based on trials and clinical experience

1.2. Systolic versus diastolic heart failure

Heart failure is usually associated with evidence of left ventricular (LV) systolic dysfunction, although diastolic impairment at rest is a common if not universal accompaniment. Diastolic heart failure is often presumed to be present when symptoms and signs of heart failure occur in the presence of a preserved LV systolic function.

1.3. Diagnosis of chronic heart failure

- Heart failure is a syndrome where the patients should have the following features; symptoms of heart failure, typically breathlessness or fatigue, either at rest or during exertion, or ankle swelling and objective evidence of cardiac dysfunction at

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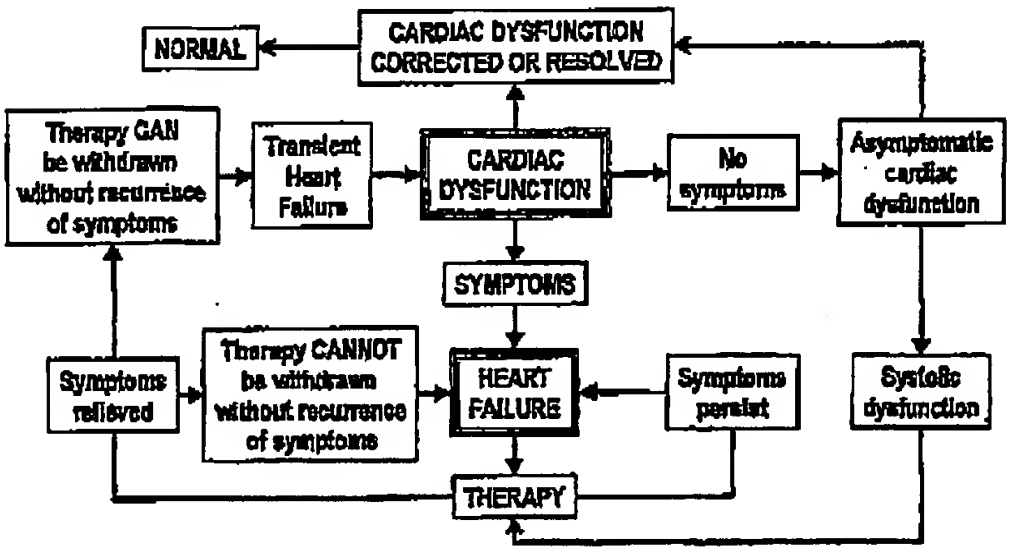

Fig. 1. Relationship between cardiac dysfunction, heart failure and heart failure rendered asymptomatic.

rest. A clinical response to treatment directed at heart failure alone is supportive but not sufficient for the diagnosis. Fig. 1 presents the relationship between different clinical manifestations of heart failure

- Heart failure should never be the final diagnosis.

The aetiology of heart failure and the presence of exacerbating factors or other diseases that may have an important influence on management should be considered carefully in all cases.

1.4. Importance of identifying potentially reversible exacerbating factors

Symptoms of chronic heart failure, pulmonary oedema and shock may be caused by tachy- and bradyarrhythmias or myocardial ischaemia even in patients without major, permanent cardiac dysfunction. It is important to identify any reversible factors in order to treat heart failure optimally.

1.5. Symptoms and signs in the diagnosis of heart failure

- Fatigue, dyspnoea and peripheral oedema are typical symptoms and signs of heart failure, but not necessarily specific. The clinical suspicion of heart failure must be confirmed by more objective tests particularly aimed at assessing cardiac function. (Fig. 2)
- There is a poor relationship between symptoms and the severity of cardiac dysfunction and between symptoms and prognosis.

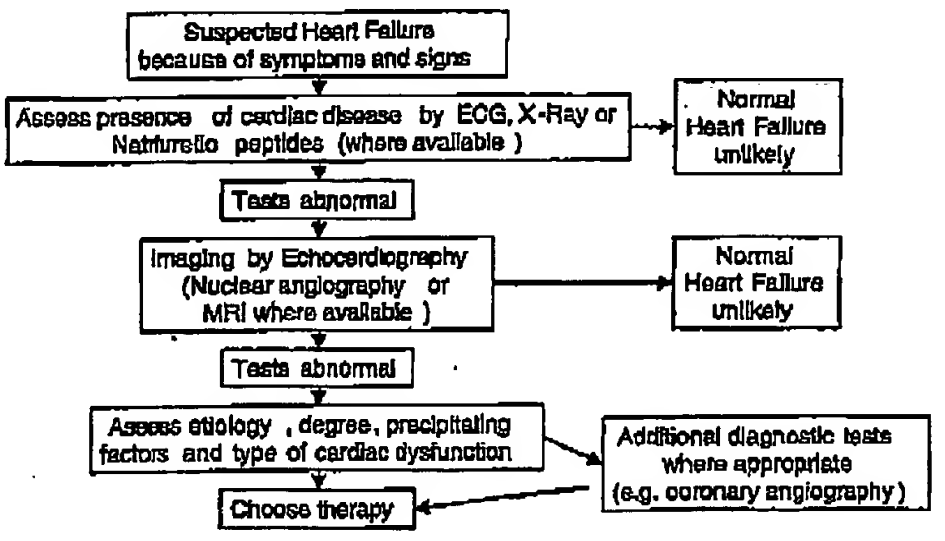

Fig. 2. Algorithm for the diagnosis of heart failure.

Once a diagnosis of heart failure has been established symptoms may be used to classify the severity of heart failure, e.g. by NYHA class or into mild, moderate or severe and should be used to monitor the effects of therapy.

1.6. Electrocardiogram

- A normal ECG suggests that the diagnosis of chronic heart failure should be carefully reviewed.

Electrocardiographic changes in patients with heart failure are frequent. The negative predictive value of normal ECG to exclude LV systolic dysfunction exceeds 90%

1.7. The chest X-ray

- Chest X-ray should be part of the initial diagnostic work-up in heart failure. It is useful to detect cardiomegaly and pulmonary congestion; however, it has only predictive value in the context of typical signs and symptoms and an abnormal ECG.

1.8. Haematology and biochemistry

- Routine diagnostic evaluation of patients with chronic heart failure includes: complete blood count (Hb, leukocytes, platelets), *S*-electrolytes, *S*-creatinine, *S*-glucose, *S*-hepatic enzymes and urinalysis. In acute exacerbations exclude acute myocardial infarction by myocardial specific enzyme analysis.

1.9. Echocardiography

- Objective evidence of cardiac dysfunction at rest is necessary for the diagnosis of heart failure. Echocardiography is the preferred method.

The most important parameter of ventricular function is the LV ejection fraction for distinguishing patients with cardiac systolic dysfunction and those with preserved systolic function. Echocardiography also provides rapid and semi-quantitative assessment of valvular function, cardiac filling characteristics through Doppler measurements, and is helpful in determining the etiology of heart failure.

1.10. Additional non-invasive tests to be considered

In patients where echocardiography at rest has not provided enough information and in severe or refractory chronic heart failure and coronary artery disease, further non-invasive imaging may include:

Stress echocardiography
Nuclear cardiology
Cardiac magnetic resonance imaging (CMR)

1.11. Pulmonary function

- Measurements of lung function are of little value in diagnosing chronic heart failure. However, they are useful in excluding respiratory causes of breathlessness.

1.12. Exercise testing

- In clinical practice exercise testing is of limited value for the diagnosis of heart failure. However, a normal maximal exercise test, in a patient not receiving treatment for heart failure, excludes heart failure as a diagnosis. Exercise testing in chronic heart failure may be useful for prognostic stratification.

1.13. Invasive investigation

- Invasive investigation is generally not required to establish the presence of chronic heart failure but may be important in elucidating the cause in individual patients (e.g. endomyocardial biopsy) or to obtain prognostic information.

Coronary angiography and hemodynamic monitoring should be considered in patients with acute or acutely decompensated chronic heart failure and in the presence of severe heart failure (shock or acute pulmonary oedema) not responding to initial treatment. Routine hemodynamic monitoring should not be used to tailor therapy in chronic heart failure

1.14. Natriuretic peptides

- Plasma concentrations of certain natriuretic peptides can be helpful in the diagnostic process, especially in untreated patients.

These peptides may be most useful clinically as a 'rule out' test due to consistent and very high negative predictive values.

1.15. Other neuroendocrine evaluations

- Other tests of neuroendocrine activation are not

Table 1
Assessments to be performed routinely to establish the presence and likely cause of heart failure

Assessments	The diagnosis of heart failure			Suggests alternative or additional diagnosis
	Necessary for	Supports	Opposes	
Appropriate symptoms	+++		+++ (If absent)	
Appropriate signs		+++	+ (If absent)	
Cardiac dysfunction on imaging (usually echocardiography)	+++		+++ (If absent)	
Response of symptoms or signs to therapy		+++	+++ (If absent)	
ECG			+++ (If normal)	
Chest X-ray		If pulmonary congestion or cardiomegaly	+ (If normal)	Pulmonary disease
Full blood count				Anaemia/Secondary polycythaemia
Biochemistry and urinalysis				Renal or hepatic disease/diabetes
Plasma concentration of natriuretic peptides in untreated patients (where available)		+ (If elevated)	+++ (If normal)	

+, of some importance; +++, of great importance.

recommended for diagnostic or prognostic purposes in individual patients.

1.16. Holter electrocardiography (ambulatory ECG, long time ECG recording — LTER)

- Conventional Holter monitoring is of no value in the diagnosis of chronic heart failure, though it may detect and quantify the nature, frequency, and duration of atrial and ventricular arrhythmias which could be causing or exacerbating symptoms of heart failure. Ambulatory electrocardiographic monitoring should be restricted to patients with chronic heart failure and symptomatic arrhythmias.

1.17. Requirements for the diagnosis of heart failure in clinical practice

To satisfy the definition of heart failure, symptoms and/or signs of heart failure and objective evidence of cardiac dysfunction, preferably obtained by echocardiography, must both be present. Conditions which mimic or exacerbate the symptoms and signs of heart failure need to be excluded (Table 1). Fig. 2 presents a diagnostic scheme to be performed routinely in patients with suspected heart failure. Additional tests (Table 2) should be performed or re-evaluated in cases where diagnostic doubt persists or clinical features suggest a reversible cause for heart failure.

Table 2
Additional tests to be considered to support the diagnosis or to suggest alternative diagnoses

Tests	The diagnosis of heart failure		Suggests alternative or additional diagnosis
	Supports	Opposes	
Exercise Test	+ (If impaired)	+++ (If normal)	
Pulmonary function tests			Pulmonary disease
Thyroid function tests			Thyroid disease
Invasive investigation and angiography			Coronary artery disease, ischemia
Cardiac output	+++ (If depressed at rest)	+++ (If normal; especially during exercise)	
Left atrial pressure	+++ (If elevated at rest)	+++ (If normal; in absence of therapy)	

+, of some importance; +++, of great importance.

Table 3
Management outline

1	Establish that the patient has heart failure
2	Ascertain presenting features: pulmonary oedema, exertional breathlessness, fatigue, peripheral oedema
3	Assess severity of symptoms
4	Determine aetiology of heart failure
5	Identify precipitating and exacerbating factors
6	Identify concomitant diseases relevant to heart failure and its management
7	Estimate prognosis
8	Anticipate complications
9	Counsel patient and relatives
10	Choose appropriate management
11	Monitor progress and manage accordingly

Table 3 provides a management outline which connects the diagnosis part of the guidelines with the treatment section.

2. Treatment of heart failure

The aims of treatment in heart failure are:

1. Prevention — a primary objective:
   - Prevention and/or controlling of diseases leading to cardiac dysfunction and heart failure.
   - Prevention of progression to heart failure once cardiac dysfunction is established.
2. Maintenance or improvement in quality of life.
3. Improved survival.

2.1. Management of chronic heart failure

The therapeutic approach in chronic heart failure due to cardiac systolic dysfunction consists of general advice and other non-pharmacological measures, pharmacological therapy, mechanical devices and surgery.

2.2. Non-pharmacological management

General advice and measures (Table 4)
Level C for all advice and measures unless stated otherwise
Rest, exercise and exercise training (Table 4)
Level C for all recommendations unless stated otherwise

2.3. Pharmacological therapy: angiotensin-converting enzyme inhibitors

- ACE inhibitors are recommended as first-line therapy in patients with a reduced LV systolic function expressed as a subnormal ejection fraction, i.e. < 40–45 (level A). Asymptomatic patients with LV systolic dysfunction benefit from long-term ACE inhibition (level A). All patients with symptomatic heart failure due to systolic LV dysfunction should receive an ACE inhibitor (level A). In the absence of fluid retention, ACE inhibitors should be given first. In patients with fluid retention together with diuretics (level B).
- ACE inhibitors should be uptitrated to the dosages shown to be effective in the large, controlled trials in heart failure (level A), and not titrated based on symptomatic improvement alone (level C) — see full text for dosages.

Important adverse effects associated with ACE inhibitors are hypotension, syncope, renal insufficiency, hyperkalaemia and angioedema.

Changes in systolic and diastolic blood pressure and increases in serum creatinine are usually small in normotensive patients.

Initiating ACE inhibitor therapy (Table 5)

2.4. Diuretics

2.4.1. Loop diuretics, thiazides and metolazone

- Diuretics are essential for symptomatic treatment when fluid overload is present and manifest as pulmonary congestion or peripheral oedema (level A), although there are no controlled, randomised trials that have assessed the effect on survival of these agents. The use of diuretics results in rapid improvement of dyspnoea and increased exercise tolerance (level B).
- Diuretics should always be administered in combination with ACE inhibitors if possible (level C).

Detailed recommendations and major side effects are outlined in Table 6.

2.5. Potassium-sparing diuretics

- Potassium-sparing diuretics should only be pre-

Table 4
General advice and measures

General advice	•Explain what heart failure is and why symptoms occur •Causes of heart failure •How to recognize symptoms •What to do if symptoms occur •Self-weighing •Rationale of treatments •Importance of adhering to pharmacological and non-pharmacological prescriptions •Refrain from smoking — use of nicotine replacement therapies •Prognosis
Drug counselling	•Effects •Dose and time of administration •Side effects and adverse effects •Signs of intoxication •What to do in case of skipped doses •Self-management
Rest and exercise	•Rest — not encouraged in stable conditions •Work •Daily physical and leisure activities in stable patients to prevent muscle deconditioning •Sexual activity •Rehabilitation — exercise training programmes in stable NYHA II/III — see full text for details
Vaccinations	•advice on immunisations
Travel	•advice on possible problems with long flights and severe heart failure, high altitudes, hot humid climates and diuretic/vasodilator use
Dietary and social habits	•Control sodium intake when necessary, e.g. some patients with severe heart failure •Avoid excessive fluids in severe HF •Avoid excessive alcohol intake

scribed if persisting hypokalaemia despite ACE inhibition or, in severe heart failure despite the combination ACE inhibition and low-dose spironolactone (level C).

- Potassium supplements are less effective in this situation (level B) (Table 6).

Table 5
The recommended procedure for starting an ACE inhibitor

1	Review the need for and dose of diuretics and vasodilators
2	Avoid excessive diuresis before treatment. Reduce or withhold diuretics, if being used, for 24 h.
3	It may be advisable to start treatment in the evening, when supine, to minimize the potential negative effect on blood pressure, although there are no data in heart failure to support this (evidence C). When initiated in the morning, supervision for several hours with blood pressure control is advisable.
4	Start with a low dose and build up to recommended maintenance dosages shown to be effective in large trials (see full text)
5	If renal function deteriorates substantially, stop treatment.
6	Avoid potassium-sparing diuretics during initiation of therapy.
7	Avoid non-steroidal anti-inflammatory drugs (NSAIDs).
8	Check blood pressure, renal function and electrolytes 1–2 weeks after each dose increment, at 3 months and subsequently at 6 monthly intervals.

The following patients should be referred for specialist care:

1	Cause of heart failure unknown
2	Systolic blood pressure < 100 mmHg
3	Serum creatinine > 150 μmol/l
4	Serum sodium < 135 mmol/l
5	Severe heart failure
6	Valve disease as primary cause

Table 6
Diuretics

Initial diuretic treatment	Loop diuretics or thiazides. Always administered in addition to an ACE inhibitor If GFR < 30 ml/min do not use thiazides, except as therapy prescribed synergistically with loop diuretics.
Insufficient response	Increase dose of diuretic Combine loop diuretics and thiazides With persistent fluid retention: administer loop diuretics twice daily In severe chronic heart failure add metolazone with frequent measurement of creatinine and electrolytes
Potassium-sparing diuretics: triamterene, amiloride, spironolactone	Use only if hypokalaemia persists after initiation of therapy with ACE inhibitors and diuretics. Start 1-week low-dose administration, check serum potassium and creatinine after 5–7 days and titrate accordingly. Recheck every 5–7 days until potassium values are stable

GFR, glomerular filtration rate; CHF, chronic heart failure; ACE, angiotensin converting-enzyme.

2.6. *Beta-adrenoceptor antagonists*

- Beta-blocking agents are recommended for the treatment of all patients with stable, mild, moderate and severe heart failure and reduced LV ejection fraction, in NYHA class II–IV, on standard treatment, including diuretics and ACE inhibitors, unless there is a contraindication (level A).
- In patients with LV systolic dysfunction, with or without symptomatic heart failure, following an acute myocardial infarction long term beta-blockade is recommended in addition to ACE inhibition to reduce mortality (level B).

Initiation of therapy — see Table 7

2.7. *Aldosterone receptor antagonists — spironolactone*

- Aldosterone antagonism is recommended in advanced heart failure (NYHA III–IV), in addition to ACE inhibition and diuretics to improve survival and morbidity (level B). Administration and dosing are shown in Table 8.

2.8. *Angiotensin II receptor antagonists (ARBs)*

- ARBs could be considered in patients who do not tolerate ACE inhibitors for symptomatic treatment (level C).
- However, it is unclear whether ARBs are as effective as ACE inhibitors for mortality reduction (level B).
- In combination with ACE inhibition, ARBs may improve heart failure symptoms and reduce hospitalisations for worsening heart failure (level B).

Whether concomitant beta-blockade negatively affects the effect of ARB needs further evaluation

2.8.1. *Safety and tolerability*

Side effects, notably cough are significantly less than with ACE-inhibitors.

2.9. *Cardiac glycosides*

- Cardiac glycosides are indicated in atrial fibrillation and any degree of symptomatic heart failure, whether or not LV dysfunction is the cause, in order to slow ventricular rate, thereby improving ventricular function and symptoms (level B). A combination of digoxin and beta-blockade appears superior than either agent alone (level C).
- In sinus rhythm, digoxin is recommended to improve the clinical status of patients with persisting heart failure symptoms due to left ventricular systolic dysfunction despite ACE inhibitor and diuretic treatment (level B).

Contraindications: bradycardia, second- and third-degree AV-block, sick sinus syndrome, carotid sinus syndrome, hypokalaemia and hypercalcaemia.

2.9.1. *Digoxin*

The usual daily dose of oral digoxin is 0.25–0.375 mg if serum creatinine is in the normal range (in the elderly 0.625–0.125 mg, occasionally 0.25 mg). No loading dose is needed when treating chronic conditions. The treatment can be initiated with 0.25 mg bid. for 2 days.

2.10. *Vasodilator agents in chronic heart failure*

- There is no specific role for vasodilators in the

Table 7
The recommended procedure for starting a beta-blocker

Patients should be on a background therapy with ACE inhibition, if not contraindicated.
The patient should be in a relatively stable condition, without the need of intravenous inotropic therapy and without signs of marked fluid retention
Start with a very low dose and titrate up to maintenance dosages shown to be effective in large trials. The dose may be doubled every 1–2 weeks if the preceding dose was well tolerated. Most patients can be managed as out-patients.

Transient worsening failure, hypotension or bradycardia may occur during the titration period or thereafter
- Monitor the patient for evidence of heart failure symptoms, fluid retention, hypotension and bradycardia
- If worsening of symptoms, first increase the dose of diuretics or ACE-inhibitor; temporarily reduce the dose of beta-blockers if necessary
- If hypotension, first, reduce the dose of vasodilators; reduce the dose of the beta-blocker if necessary
- Reduce or discontinue drugs that may lower heart rate in presence of bradycardia; reduce dose of beta-blockers if necessary, but discontinue only if clearly necessary.
- Always consider the reintroduction and/or uptitration of the beta-blocker when the patient becomes stable

If inotropic support is needed to treat a decompensated patient on beta-blockade, phosphodiesterase inhibitors should be preferred because their haemodynamic effects are not antagonized by beta-blocker agents.

The following patients should be referred for specialist care
- Severe heart failure class III/IV
- Unknown etiology
- Relative contraindications: bradycardia, low blood pressure
- Intolerance to low dose beta-blockade
- Previous use of beta-blocker and discontinuation because of symptoms
- Suspected asthma or bronchial disease

Contraindications to beta-blockers in patients with heart failure
- Asthma bronchiale
- Severe bronchial disease
- Symptomatic bradycardia or hypotension

treatment of heart failure (level A), although they may be used as adjunctive therapy for angina or concomitant hypertension (level C).
- In case of intolerance for ACE inhibitors ARBs are preferred to the combination hydralazine–nitrates (level A).
- In general, calcium antagonists are not recommended for the treatment of heart failure due to systolic dysfunction.

2.11. Positive inotropic therapy

- Inotropic agents are commonly used to limit severe episodes of heart failure or as a bridge to heart transplantation in end-stage heart failure (level C). However, treatment-related complications may occur and their effect on prognosis is not well recognised
- Repeated or prolonged treatment with oral inotropic agents increases mortality (level A).
- Currently, insufficient data are available to recommend dopaminergic agents for heart failure treatment.

2.12. Anti-thrombotic agents

- There is little evidence to show that anti-thrombotic therapy modifies the risk of death, or vascular events in patients with heart failure other than in

Table 8
Administration and dosing considerations with spironolactone

1	Consider whether a patient is in severe heart failure (NYHA III–IV) despite ACE inhibition/diuretics
2	Check serum potassium (< 5.0 mmol/l) and creatinine (< 250 μmol/l)
3	Add 25 mg spironolactone daily
4	Check serum potassium and creatinine after 4–6 days
5	If at any time serum potassium > 5–5.5 < mmol/l, reduce dose by 50%. Stop if serum potassium > 5.5mmol/l.
6	If after 1 month symptoms progress and normokalemia exists, increase to 50 mg daily. Check serum potassium/creatinine after 1 week.

the setting of atrial fibrillation when anti-coagulation is firmly indicated (level C).

2.13. Antiarrhythmics

- In general, there is no indication for the use of anti-arrhythmic agents in heart failure (level C).

2.13.1. Class I anti-arrhythmics

Class I anti-arrhythmics should be avoided (level C).

2.13.2. Class II anti-arrhythmics

Beta-blockers reduce sudden death in heart failure (level A).

They may be indicated in the management of sustained or non-sustained ventricular tachy-arrhythmias, either alone or in combination with amiodarone or non-pharmacological therapy (level C).

2.13.3. Class III anti-arrhythmics

Amiodarone is effective against most supraventricular and ventricular arrhythmias (level B). But routine administration of amiodarone in patients with heart failure is not justified (level B).

2.14. Devices and surgery: revascularisation procedures, mitral valve surgery, cardiomyoplasty and partial left ventriculotomy

- Surgical treatment should be directed towards the underlying etiology and mechanisms. In addition to revascularisation, it is important to approach patients with significant valvular disease, e.g. aortic stenosis, before they develop significant LV dysfunction.

2.14.1. Revascularisation

There are no controlled data to support the use of revascularisation procedures for the relief of heart failure symptoms, but in individual patients with heart failure of ischaemic origin revascularisation may lead to symptomatic improvement (level C).

2.14.2. Mitral valve surgery

Mitral valve surgery in patients with severe left ventricular dysfunction and severe mitral valve insufficiency may lead to symptomatic improvement in selected heart failure patients (level C).

Cardiomyoplasty and partial left ventriculotomy (Batista procedure) cannot be recommended for the treatment of heart failure (level C).

2.15. Pacemakers

- Pacemakers have no established role in the treatment of heart failure except for conventional bradycardia indication.
- Resynchronisation therapy using bi-ventricular pacing may improve symptoms and sub-maximal exercise capacity (level B), but its effect on mortality and morbidity is as yet unknown.

2.16. Arrhythmia devices and surgery

2.16.1. Implantable cardioverter defibrillators (ICD)

- There is as yet no specifically defined role for ICD in chronic heart failure (level C) as available data from controlled trials have not specifically addressed its effect in heart failure patients

2.17. Heart transplantation, ventricular assist devices and artificial heart

2.17.1. Heart transplantation

- Heart transplantation is an accepted mode of treatment for end stage heart failure. Although controlled trials have never been conducted, it is considered to significantly increase survival, exercise capacity, return to work and quality of life compared to conventional treatment, provided proper selection criteria are applied (level C).

2.17.2. Ventricular assist devices and artificial heart

Current indications for ventricular assist devices and artificial heart include bridging to transplantation, transient myocarditis and in some permanent hemodynamic support (level C).

2.18. Choice and timing of pharmacological therapy of heart failure due to systolic LV dysfunction

- Before initiating therapy, the correct diagnosis needs to be established and considerations should be given to the Management Outline presented in Table 3 (see also Table 9).

2.19. Asymptomatic systolic LV dysfunction

Treatment with an ACE inhibitor is recommended

Table 9
Chronic heart failure —choice of pharmacological therapy

LV systolic dysfunction	ACE inhibitor	Diuretic	Beta-blocker	Aldosterone antagonists	Cardiac glycosides
Asymptomatic LV dysfunction	Indicated	Not indicated	Post MI	Not indicated	With atrial fibrillation
Symptomatic HF (NYHA II)	Indicated	Indicated if fluid retention	Indicated	Not indicated	(a) When atrial fibrillation; (b) when improved from more severe HF in sinus rhythm
Worsening HF (NYHA III–IV)	Indicated	Indicated, combination of diuretics	Indicated (under specialist care)	Indicated	Indicated
End-stage HF (NYHA IV)	Indicated	Indicated, combination of diuretics	Indicated (under specialist care)	Indicated	Indicated

HF, heart failure; LV, left ventricular; MI, myocardial infarction.

in patients with reduced systolic function as indicated by a substantial reduction in left ventricular ejection fraction. In patients with asymptomatic left ventricular dysfunction following an acute myocardial infarction add a beta-blocker.

2.20. Symptomatic systolic LV dysfunction-heart failure NYHA class II

Without signs of fluid retention: ACE inhibitor — titrate to the recommended target doses. Add a beta-blocker and titrate to target dosages (see full text for target dosages of ACE inhibitors and beta-blockers). If patients remain symptomatic (Fig. 3):

- Consider alternative diagnosis.
- When ischaemia is suspected, consider nitrates or revascularisation before adding a diuretic.
- Add a diuretic.

With signs of fluid retention — diuretics in combination with an ACE inhibitor and a beta-blocker: first, the ACE inhibitor and diuretic should be co-administered. When symptomatic improvement occurs, i.e. fluid retention disappears, try to reduce the dose of diuretic, but the optimal dose of the ACE inhibitor should be maintained. To avoid hyperkalaemia, any potassium-sparing diuretic should be omitted from the diuretic regimen before introducing an ACE inhibitor. Potassium-sparing diuretics may be added if hypokalaemia persists. Add a beta-blocker and titrate to target dosages. Patients in sinus rhythm receiving

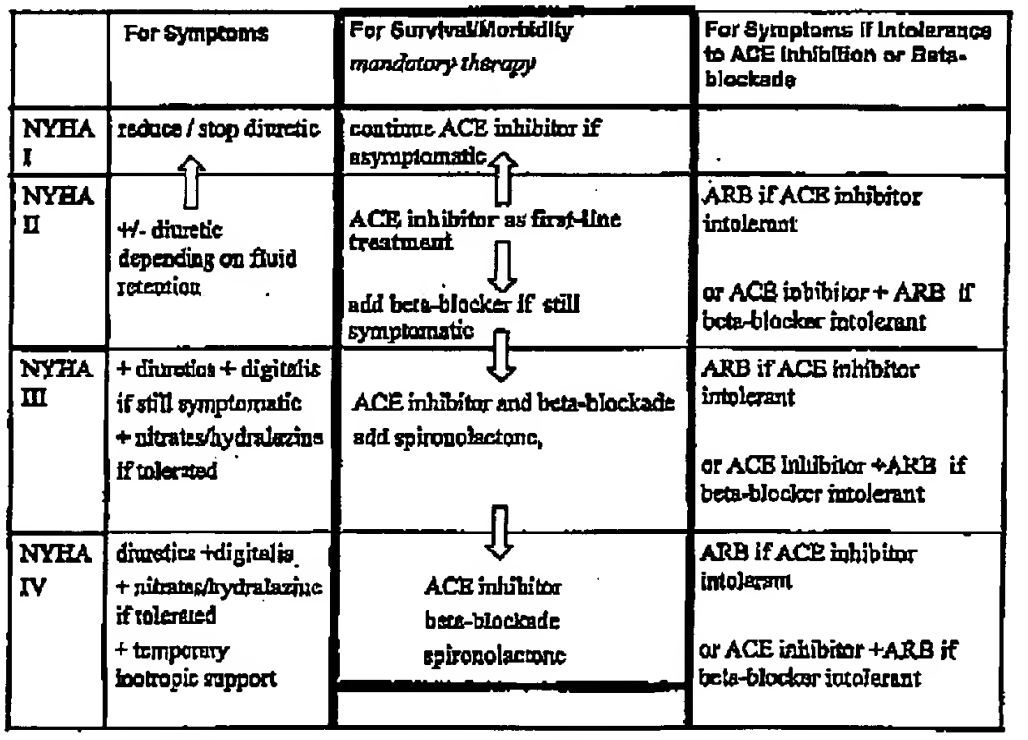

Fig. 3. Pharmacological therapy of symptomatic chronic heart failure due to systolic left ventricular dysfunction.

cardiac glycosides, who have improved from severe to mild heart failure, should continue cardiac glycoside therapy. In case of intolerance to ACE inhibition or beta-blockade, consider addition of an ARB to the remaining drug. Avoid adding an ARB to the combination ACE inhibitor and a beta-blocker.

2.21. *Worsening heart failure*

For most frequent causes of worsening heart failure see full text. Patients in NYHA class III who have improved from NYHA class IV during the preceding 6 months or are currently NYHA class IV should receive low-dose spironolactone (12.5–50 mg daily, Table 8). Cardiac glycosides are often added. Loop diuretics can be increased in dose. Combinations of diuretics (a loop diuretic with a thiazide) are often helpful (Fig. 3). Consider cardiac transplantation

2.22. *End stage heart failure (patients who persist in NYHA IV despite optimal treatment and proper diagnosis*

Patients should be (re)considered for heart transplantation. Consider palliative treatment in terminal patients, e.g. opiates for the relief of symptoms (Fig. 3).

2.23. *Management of heart failure due to diastolic dysfunction*

There is little evidence from clinical trials or observational studies as to how to treat diastolic dysfunction, and there is uncertainty about the prevalence of diastolic dysfunction in patients with heart failure symptoms and a normal systolic function in the community.

2.24. *Pharmacotherapy of diastolic heart failure*

The recommendations provided below are largely speculative, as limited data exist in patients with preserved LV systolic function or diastolic dysfunction (level C), patients being excluded from nearly all large controlled trials in heart failure.

1. Beta-blockade to lower heart rate and increase the diastolic period.
2. Verapamil-type calcium antagonists may be used for the same reason. Verapamil may lead to a functional improvement in patients with hypertrophic cardiomyopathy.
3. ACE inhibitors may improve relaxation and cardiac distensibility directly, may have a long-term effect through regression of hypertrophy and reduce hypertension.
4. Diuretics may be necessary when episodes with fluid overload are present, but should be used cautiously so as not to lower preload excessively and thereby reduce stroke volume and cardiac output.

2.25. *Heart failure treatment in the elderly*

The therapeutic approach to systolic dysfunction in the elderly should be principally identical to that in younger heart failure patients with respect to the choice of drug treatment.

2.26. *Arrhythmias*

- In the approach to arrhythmia it is essential to recognise and correct precipitating factors, improve cardiac function and reduce neuro-endocrine activation with beta-blockade, ACE inhibition and possibly aldosterone receptor antagonists (level C).

2.26.1. *Ventricular arrhythmias*

- In patients with ventricular arrhythmias, the use of antiarrhythmic agents is only justified in patients with severe, symptomatic, sustained ventricular tachycardias and amiodarone should be the preferred agent (level B).

2.26.2. *Atrial fibrillation*

- For persistent (non self-terminating) atrial fibrillation, electrical cardioversion should always be considered, although its success rate may depend on the duration of atrial fibrillation and left atrial size.

There is no evidence in patients with persistent atrial fibrillation and heart failure suggesting that restoring and maintaining sinus rhythm is superior to control of heart rate.

In permanent (cardioversion not attempted or failed) atrial fibrillation, rate control is mandatory.

In asymptomatic patients, beta-blockade, digitalis glycosides or the combination may be considered, in symptomatic patients digitalis glycosides are the first choice (level C). If digoxin or warfarin is used in

combination with amiodarone, their dosages may need to be adapted.

2.27. Symptomatic systolic left ventricular dysfunction and concomitant angina or hypertension

Specific recommendations in addition to general treatment for heart failure due to systolic left ventricular dysfunction.

If angina is present:

1. Optimise existing therapy, e.g. beta-blockade.
2. Consider coronary revascularisation.
3. Add long-acting nitrates.
4. If not successful: add second generation dihydropyridine derivatives.

If hypertension is present:

1. Optimise dose ACE inhibitors, beta-blocking agents and diuretics.
2. Add spironolactone or ARBs if not present already.
3. If not successful: try second generation dihydropyridine derivatives.

2.28. Care and follow-up

Comprehensive non-pharmacological intervention programmes are helpful in improving quality of life, reducing readmission and decreasing cost (level of evidence B).

However, it is unclear what the best content of organisation of these programs is. Different models (e.g. heart failure outpatient clinic, heart failure nurse specialist, community nurse specialist, patient telemonitoring) may be appropriate depending on the stage of the disease, patient population and national resources (level of evidence C).

Although basic agreement can be achieved on the content of care needed by patients with heart failure, the organisation of the care should be closely adapted to the needs of the patient group and the resources of the organisation.

References

[1] Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Guidelines for the Diagnosis and Treatment of Chronic Heart Failure. Eur Heart J 2001;22:1527–60.

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Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials

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Abstract

Objective: To summarise the current evidence from randomised controlled trials for diuretics in patients with congestive heart failure (CHF). *Data sources:* English-language randomised controlled trials and review papers referenced in Medline, Embase between 1966 and 1999. General literature review of pertinent journals was carried out and reference lists of papers were inspected. *Review method: study design*: Meta-analysis of randomised controlled trials of diuretic therapy in patients with CHF. *Study selection:* Studies were included if they were randomised comparisons of loop or thiazide diuretics and control, or one diuretic and another active agent (e.g. ACE inhibitors, ibopamine and digoxin). *Data abstraction:* Using a standardised protocol, two reviewers independently abstracted the data and assessed the methodological quality of each paper. *Data synthesis:* The odds ratio (OR) of treated group compared with control was estimated for each end-point outcome and plotted against each other using the fixed-effects model. The main outcome measures: The primary outcomes of our analysis were effects of diuretics on mortality and morbidity. *Results:* Eighteen trials met our criteria and were eligible for analysis, involving 928 patients. Eight trials were placebo-controlled. We analysed the data for mortality and for worsening heart failure. A further ten trials compared diuretics against other agents such as ACE inhibitors, ibopamine, and digoxin. Mortality data were available in three of the placebo-controlled trials (n=221); the mortality rate was lower for patients treated with diuretics than for control [the odds ratio for death, 0.25; 95% confidence intervals (CI), 0.07–0.84; P=0.03]. Admissions for worsening heart failure in the four small trials (n=448) showed an odds ratio of 0.31 (95% CI 0.15–0.62; P=0.001). In six studies of diuretics compared to active control, diuretics significantly improved exercise capacity in patients with CHF [OR: 0.37; CI: 0.10–0.64, P=0.007]. *Conclusion:* Compared to active control, diuretics appear to reduce the risk of worsening disease and improve exercise capacity. The available data from small studies show that in CHF conventional diuretics reduce the risk of death and worsening heart failure compared to placebo.

Keywords: Congestive heart failure; Cardiac failure; Diuretics; Treatment; Randomised controlled trials; Observational studies and reviews

1. Introduction

Congestive heart failure (CHF) is a major cause of morbidity and mortality worldwide. During the last 2 decades clinical trials have shown that use of angiotensin-converting enzyme (ACE) inhibitors [1–3], and more recently β-blockers [4,5] reduce mortality and morbidity in CHF.

Diuretics are regarded as the first-line treatment for patients with CHF since they provide symptomatic relief [6–8]. Despite widespread clinical acceptance of the use of diuretics, there is uncertainty about their precise therapeutic efficacy because there are no large trials comparable to those of ACE inhibitors [1–3] and β-blockers [4,5]. Diuretics reduce pulmonary

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congestion in patients with heart failure, but their effects on disease progression and survival remain unclear [9,10]. We conducted a meta-analysis to summarise the current evidence for conventional diuretic therapy in patients with heart failure based on data from published randomised controlled trials to determine whether there were any effects on clinical outcomes.

2. Methods

Randomised trials of loop or thiazide diuretic therapy in patients with CHF were identified by performing a Medline and Embase search referenced between 1966 and 1999. The search was carried out using the following keywords: heart failure; congestive heart failure; cardiac failure; diuretics; treatment; trials; randomised controlled trials; controlled trials; observational studies and reviews. Hand searching of pertinent journals was carried out and reference lists of papers were inspected. The search focused on randomised and controlled trials and review papers published between 1938 and 1999. Book chapters and editorials were also scanned. Uncontrolled and non-randomised studies were not included. Two reviewers assessed the methodological quality of each paper. Only randomised and controlled trials were included in the review. Clinical trials were classified according to whether an inactive or active agent was used in the control group.

2.1. Study design

Meta-analysis of randomised controlled trials of diuretic therapy in patients with CHF.

2.2. Main outcome measures

The primary intention was to obtain data on mortality and morbidity from each published randomised controlled trial of any diuretic agent in patients with heart failure. As this information was lacking in many trials, five other possible outcomes were evaluated where information was available: (1) effect of diuretic withdrawal on worsening of heart failure; (2) effect of diuretics on exercise capacity; (3) effect of diuretics on symptoms and quality of life; (4) haemodynamic effect of diuretics and (5) neuroendocrine effect of diuretics.

2.3. Statistical analysis

We used standard methods for the combination of information from 2×2 tables (e.g. of treated/controlled versus event/no event). We used the Mantel and Haenzel [11] method for continuous variables to measure the effect of diuretics on exercise capacity. In the meta-analysis, an informative use of these trials is to calculate the weighted average of odds ratios and to accept this as an approximate indication of risk reduction and/or improvement typically conferred by diuretics on the outcome of interest. Consequently, the odds ratio (OR) of the treated group compared with controls was estimated for each endpoint outcome and plotted against each other by using the fixed-effects model. The meta-analysis was performed with STATA statistical software package, Version 6 (Stata, College Station, TX, USA). Values of $P<0.05$ were considered statistically significant.

3. Results

Eighteen randomised controlled trials carried out from 1966 to 1999 met our criteria [16–33] (Tables 1 and 2). Four studies which did not fulfil our criteria were excluded [12–15] (Fig. 1). One of these studies was the large RALES trial [15]. This was a double-blind study of the effect of spironolactone vs. placebo on morbidity and mortality in patients with severe heart failure. We excluded RALES from our primary analyses because spironolactone is not generally considered to be a conventional diuretic, and in RALES most patients were already receiving diuretics. Since RALES was so large we performed a subsidiary analysis including this trial. Another study [21] was also excluded from the analysis because patients had lung disease and the trial was terminated prematurely for ethical reasons (50% of patients developed pulmonary oedema when diuretics were withdrawn). Eight trials were placebo controlled (n=545) [16–23] and ten were active controlled trials (n=280) [24–33].

Key features of all these trials (study design, baseline characterisation of study patients, and out-

Table 1
Outline of study population in active/placebo trials

Authors	Study design[a]	Agent tested[b]	Follow-up (weeks)	Patients completed	Mean age (years)	Male (%)	LV-performance[f]	Worsened HF	Death (%)[g]
Burr et al. [16][c]	rd, db, plac, controlled	Placebo/ diuretics+	12	89	82	14	–	5 (9.25) 0	3 (5.6)* 1 (1.9)·
Myers et al. [17][c]	rd, db, plac, controlled	Placebo/ diuretics+	52	59	82	80	–	2 (5.3%) 6 (15.4%)	7 (18.4) 2 (5.0)Φ
Mathur et al. [21][b]	rd, db, plac, cross-over	Placebo/ Furosemide-Hctz	16	5	60.3	80	EF: 64±6.8/ −51±8	5 (100%) 0	0 0
Sherman et al. [18]	rd, db, plac, parallel	Placebo/ Pentamide	4	36	59.5±2	74	–	0	2' (11) 0
Cheitlin et al. [22][c]	rd, db, plac, cross-over	Placebo/ Amiloride	12	11	63	100	PCWP; RAP LVWI; mPAP	0	0
De Jong et al. [19][c]	rd, open, controlled	Placebo/ diuretics+	8	55	75	13	–	3 (10.3%) 0	0
Barr et al[c]	rd, db, plac, parallel	Placebo/ Spironolactone	8	42	69±2	76	FS: 23±7/20±6	0	0
Walma et al. [20]	rd, db, controlled	Placebo/ diuretics+	24	139	76	26	–	24 (24.5%) 4 (4%)	0
RALES [15]	rd, db, plac, controlled	Placebo/ Spironolactone	288	850	62±12	25	EF<20%	300 (36%) 215 (26%)	386 (46) 284 (35)

[a] The aim of these trials was to study the effect of discontinuing long-term diuretic therapy in the elderly.
[b] This study was terminated prematurely because 50% of patients developed pulmonary oedema.
[c] These trials evaluated the effect of adding other diuretics (usually K-sparing agents) to conventional therapy.
[d] rd, randomised; db, double-blind; plac, placebo.
[e] +Diuretic, various agents could have been used, including furosemide; F-Hctz, furosemide-hydrochlorothiazide.
[f] PRA: plasma renin activity; PCWP; pulmonary capillary wedge pressure; LVWI: left ventricular wall index; mPAP: mean pulmonary artery pressure; A.O index: ankle oedema index; LFTs: liver function tests; ABG: arterial blood gases; RAP: right atrial pressure; VPCs: premature ventricular contractions.
[g] 1, Causes of death: carcinoma 3; respiratory disease 2; stroke, 1; gastrointestinal haemorrhage 1; Φ: causes of death were malnutrition and dementia and carcinoma.

comes) are presented in Table 1 (placebo controlled) and Table 2 (active control trials). There was information on the following outcomes: (1) effect of diuretics on mortality which was documented in three placebo controlled trials (n=221) [16–18]; (2) effect of diuretics on worsening heart failure which was documented in four placebo controlled (n=448) [16,17,19,20] and four active controlled trials (n=150) [24–27]; (3) effect of diuretics on exercise capacity which was documented in six of the active controlled trials (n=174) [24–29]. These three parameters were defined as the outcomes for this meta-analysis.

3.1. Study design and completeness of follow-up

As shown in Tables 1 and 2 the studies were designed with parallel (n=9) or cross-over (n=9) protocols. Their duration was in the range of 4–24 weeks with the exception of one trial which lasted 52 weeks. More than 85% of the patient population completed the planned follow-up period.

3.2. Patient selection and exclusion criteria

Patients were selected on the basis of symptoms, clinical and radiological findings, parameters of ventricular function or haemodynamics, or if pre-existing diuretic treatment for heart failure was required. The exclusion criteria applied in the various trials were clinically unstable conditions such as recent myocardial infarction, unstable angina pectoris and arrhythmias, hypotension or hypertension, valvular heart diseases, right heart failure or pulmonary oedema.

3.3. Baseline characterisation of study patients

Selected baseline features of patients in the 18

Table 2
Study design and characterisation of study patients in active/controlled trials

Authors	Study design[a]	Agent tested[b]	Follow-up (weeks)	Patients included	Mean age (years)	Male (%)	LV-performance[c]	Exercise tolerance 1	Exercise tolerance 2[d]	Worsened HF (%)	Death (%)
Dahstrom	rd, db, plac, cross-over	Prenalterol/ F-Sitrosulactone	4	10	70	90	FS: 14±2–15±2	92±11 W 94±12 W	~99±11 W 92±12 W	0 0	0
Bonsnstli et al. [24]	rd, db, plac, parallel	Captopril/ Furosemide	12	15	55.8	53	EDD: 63.4±6.1~ 77.0±14.7 *	9.2±3.5 min 11.12±3.6 min	13.29±7.2 min 19.06±4.4 min $P<0.01$	0 1 (12.5%)	0 0
Cowley et al. [25]	rd, db, plac, cross-over	Captopril/ Prazil	4	10	57.5	100	–	13.4±0.9 min 13.4±0.9 min	14.9±0.9 min 15.3±0.9 min P=NS	0 0	0 0
Richardson et al. [25]	rd, db, plac, parallel	Captopril/ Prazil	8	14	54±4	86	–	18.4±1.5 min 18.4±1.5 min	18.6±1.5# 18.8±1.5	4 (28.6%) 0	0 0
SK and F-Hep WG [30]	rd, db, plac, parallel	Ibopamine/ F-Hctz	6	103	NA	75	–	NA	NS	0 0	0 *1 (2.3%)
Siewer et al. [32]	rd, db, plac, cross-over	Digoxin/ Hctz-Triamterene	5	16	NA	NA	PCWP: 32±8	–	–	0 0	0 0
Hiemz et al. [29]	rd, db, plac, parallel	Digoxin/ Pentazide	NA	42	NA	NA	PCWP: 20±7–18±6	1.83±0.58 min 2.08±0.47 min	3.75±1.1** 3.25±0.92 min	0 0	0 0
Nordrehaug et al. [33]	rd, db, plac, cross-over	Bucumolol/ Hctz	6	29	58±4	72	–	–	–	0 0	0 0
Packer et al. [26]	rd, db, plac, parallel	Ibopamine/ Furosemide	6	130	56.6	81	–	12.8 min 13.6 min	=14.0±3.9 14.6±3.5 min	1 (1.5%) 1 (1.85%)	0 0
Andreas et al. [27]	rd, db, plac, cross-over	Ibopamine/ Furosemide	16	14	62.3±7.6	86	–	13.4±1.2 min 13.4±1.2 min	12.63±6.56‡ 15.0±1.2 min	4 (28.6%) 0	0 0

[a] rd, randomised; db, double-blind; dd, double-dummy.
[b] Hctz, hydrochlorothiazide.
[c] PCWP, pulmonary capillary wedge pressure; 'A', amiloride.
[d] The cause of death was myocardial infarction; **, P=NS; =, $P<0.04/<0.02$; $P<0.001$; ESC; emotional symptom complex; ~, $P<0.027/<0.01$; ‡, $P<0.05$; ϕ, exercise duration was estimated from the graph (P=NS); exercise tolerance 1: at baseline; exercise tolerance 2: after treatment.

randomised, controlled trials are shown in Tables 1 and 2. Mean age was 59±11 years, and 39% were women. About 27% of the patients were in NYHA class I, 40% in class II, 29% in class III and only a few patients were in class IV. In trials reporting parameters of left ventricular function, the ejection fraction (EF) was about 46% (range: <20–65%) and the end-diastolic dimension was increased at 68 mm (range: 63–77 mm). In trials where haemodynamic monitoring was used, the mean pulmonary capillary wedge pressure (PCWP) was elevated at 26 mmHg.

3.4. Aetiology of heart failure

Although the aetiology of heart failure was not provided in more than half of the trials, the most common cause was coronary artery disease, prior myocardial infarction, and dilated cardiomyopathy. Other less common underlying diseases were hypertension and pulmonary disease (chronic obstructive airway disease).

3.5. Study medications

The type of diuretic and the doses used in the trials varied from study to study and within the individual study. Loop diuretics (e.g. furosemide) were used in the majority of the studies. In twelve of the studies most or all of the patients were treated concomitantly with digoxin. In six of the studies patients were taking ACE inhibitors. In one study, 21% of patients were taking amiodarone [28] and in another study, 88% of patients were taking vasodilators [23].

3.6. Effect of diuretics on mortality

3.6.1. Placebo controlled trials

As shown in Table 1 only three [16–18] of the eight active controlled trials reported on the effect of

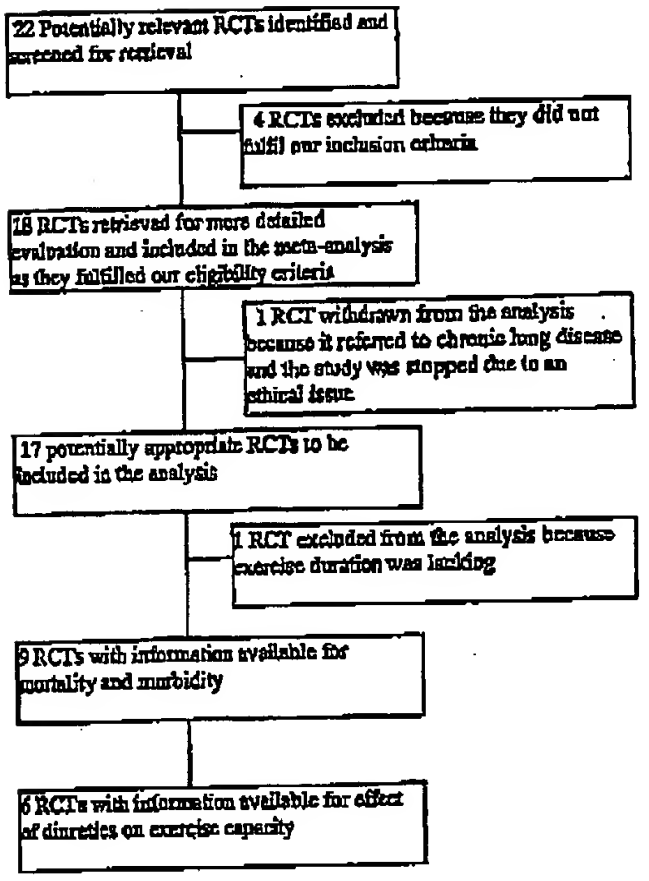

Fig. 1. Flow diagram of selection of trials for the meta analysis of the use of diuretics in congestive heart failure.

diuretic therapy on mortality in patients with heart failure. In these trials (n=221), there were 3/111 (2.7%) deaths in the diuretic group compared to 12/110 (10.9%) in the placebo group [OR, 0.25; 95% confidence intervals (CI), 0.07–0.84; P=0.03] (Fig. 2). This difference represents an absolute risk reduction of 8% in mortality in patients treated with diuretics compared to placebo (number needed to treat=12.5). If the RALES study is included [15–18], the numbers of deaths in patients randomised to diuretic compared to control were 287/933 (31%) and 398/951 (42%), the overall odds ratio was 0.61 (95% CI, 0.50–0.74; P=0.0001).

3.7. Effect of diuretics on worsening of heart failure (Table 2)

Four trials reported on the effects of diuretics on worsening heart failure [16,17,19,20] and the odds ratio for the comparison of diuretics vs. placebo was 0.31 (95% CI, 0.15–0.62; P=0.001; Fig. 3). If the RALES study [15] is included, the overall odds ratio was 0.61 (95% CI, 0.50–0.75; P=0.0001) (Fig. 3).

3.7.1. Active controlled trials

The control agents in these trials included ACE inhibitors, digoxin and ibopamine. Only four [24–27]

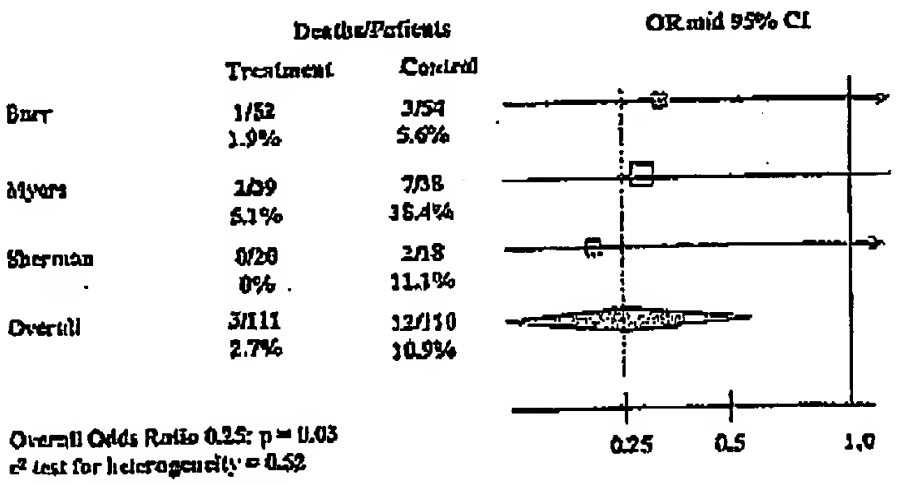

Fig. 2. Effects of diuretic therapy on mortality in patients with congestive heart failure (active/placebo trials). The odds ratios and 95% confidence intervals for each of the trials in the meta-analysis are shown. The squares represent the point estimate for the odds ratios and the longitudinal lines the 95% confidence intervals. The size of the square is approximately equal to the amount of the statistical information in the trial (statistical weight). Points to the left of the solid vertical line suggest that diuretics have a beneficial effect. The dotted vertical line represents the overall odds ratio and the diamond represents the 95% confidence interval around this.

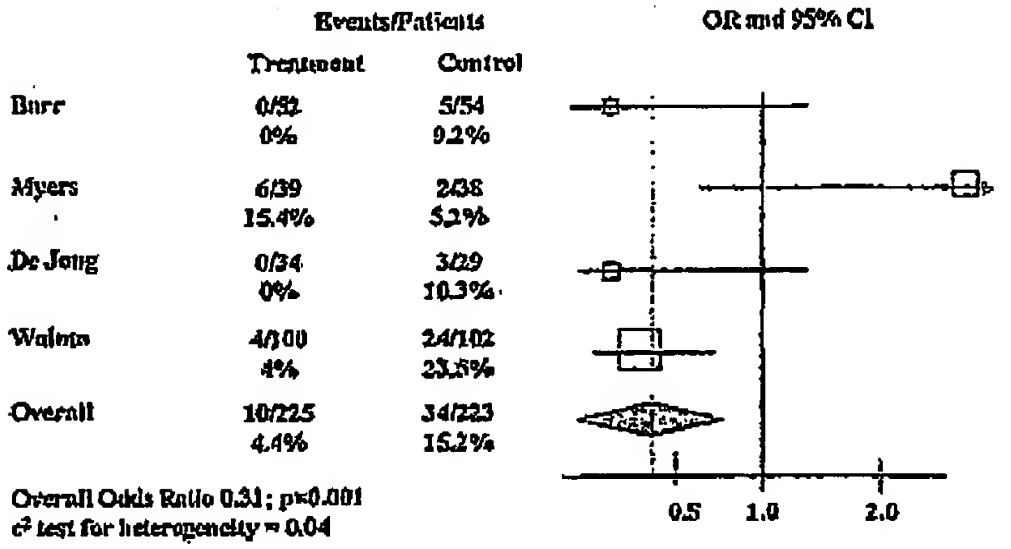

Fig. 3. Effects of diuretic withdrawal on worsening heart failure (active/placebo trials). The odds ratios and 95% confidence intervals for each of the trials in the meta-analysis are shown. The squares represent the point estimate for the odds ratios and the longitudinal lines the 95% confidence intervals. The size of the square is approximately equal to the amount of the statistical information in the trial (statistical weight). Points to the left of the solid vertical line suggest that diuretics have a beneficial effect. The dotted vertical line represents the overall odds ratio and the diamond represents the 95% confidence interval around this.

of ten trials reported the outcome parameter of the effect of diuretic on worsening of heart failure (Table 2). Plots of the estimated odds ratio and 95% confidence intervals for each trial are given in Fig. 4. The estimated overall odds ratio was 0.34 (95% CI, 0.10–1.21; P=0.10).

3.8. Effect of diuretics on exercise capacity

Seven [24–30] of the ten active controlled trials reported on the effect of diuretic therapy on exercise capacity in patients with heart failure. The trial by SK and F Ibobamine Working Group [30] was excluded

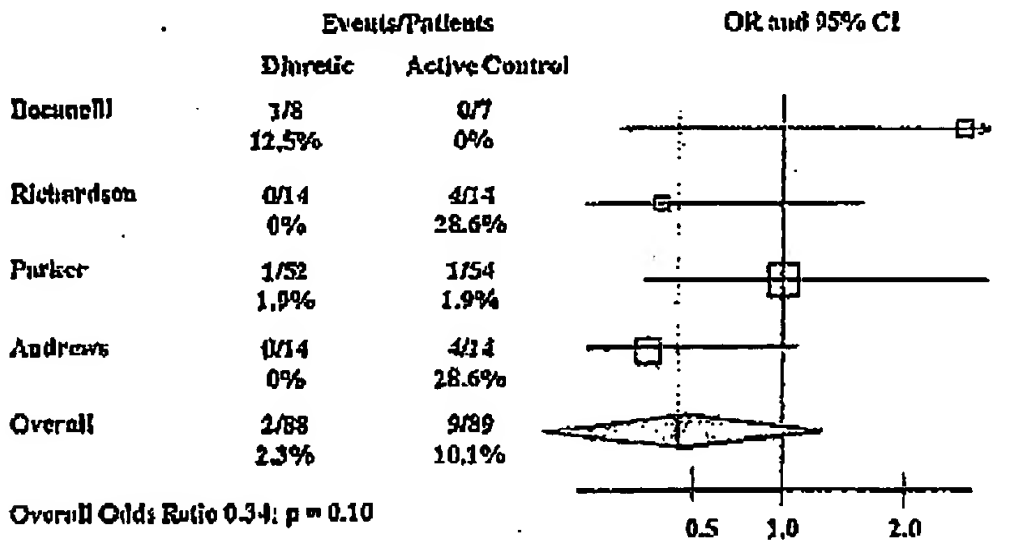

Fig. 4. Effects of diuretic withdrawal on worsening heart failure (active/controlled trials). The odds ratios and 95% confidence intervals for each of the trials in the meta-analysis are shown. The squares represent the point estimate for the odds ratios and the longitudinal lines the 95% confidence intervals. The size of the square is approximately equal to the amount of the statistical information in the trial (statistical weight). Points to the left of the solid vertical line suggest that diuretics have a beneficial effect. The dotted vertical line represents the overall odds ratio and the diamond represents the 95% confidence interval around this.

Table 3
Effect of diuretics on exercise capacity in patients with CHF

Authors	Year	Study design	Agent tested	No. of Patients gp-1 gp-2	Exercise baseline gp-1 gp-2	Duration follow-up gp-1 gp-2
Bocanelli et al. [24]	1986	db, dd, crossover	Captopril/ Furosemide	7 8	9.3±2.5 11.1±3.6	13.3±7.5 19.7±4.4
Cowley et al. [28]	1986	db, crossover	Captopril/ Frumil	10[a] 10	13.3±1.2 13.4±1.2	14.09±0.9 15.9±0.9
Richardson et al. [25]	1987	db,dd, crossover	Captopril/ Frumil	14[a] 14	17.0 17.0	18.6±1.5[b] 18.8±1.5
Haerer	1989	db, plac, parallel	Digoxin/ Perhanide	14 14	2.03±0.47 1.83±0.58	3.25±0.95 3.75±1.1
Parker et al. [26]	1993	db, plac, parallel	Ibopamine/ Furosemide	54 53	13.6 12.8	14.0±3.3 14.6±3.5
Andrews et al. [27]	1997	db, crossover	Ibopamine/ Furosemide	14[a] 14	13.4±1.2 13.4±1.2	12.6±6.6 15.0±1.2

[a] In these trials same patients were crossed to the other treatment after certain duration.
[b] Follow-up exercise duration was estimated from the graph; gp-1: control; gp-2: active.

from the analysis because information on exercise duration was lacking. Data for exercise capacity in each of the six trials are shown in Table 3. The estimated odds ratio and 95% confidence interval for each trial are shown in Fig. 5. The overall odds ratio was 0.37 (95% CI, 0.10–0.64, $P=0.007$).

4. Discussion

The principal finding of this systematic overview was that treatment with diuretic therapy produced a relative reduction in mortality of about 70% (absolute reduction of 8%) with wide confidence intervals

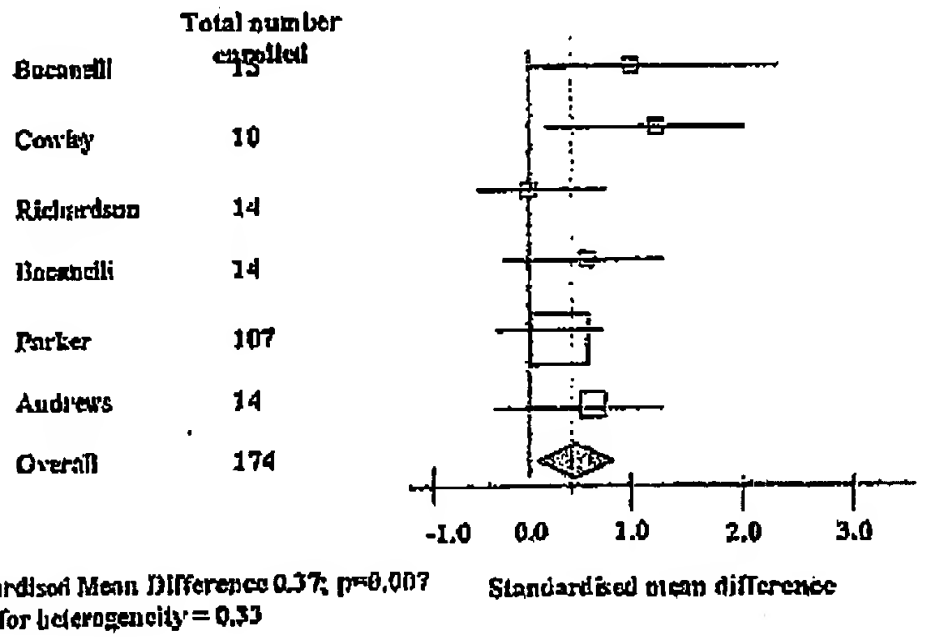

Fig. 5. Effects of diuretics on exercise capacity (active/controlled trials). In this figure, we show the comparison of the exercise capacity in the trials of diuretic compared to active control. The squares represent mean differences and the longitudinal lines the 95% confidence intervals around this. For explanation of other symbols, please refer to legend for Figs. 2–4.

compared to control in patients with heart failure. If this estimate is correct about 80 deaths could be avoided for every 1000 patients treated. We also demonstrate that diuretic therapy compared to placebo produced a similar reduction in the risk of worsening heart failure. Compared to other active agents (i.e. ACE inhibitors, digoxin or ibopamine), diuretics improved symptoms of heart failure (although this effect was not significant), and significantly increased exercise capacity by about 12%.

The mean age of the patients in the studies was 59 years, similar to the age of patients enrolled in ACE inhibitors trials [1–3] but considerably lower than the mean age of heart failure in the population which is about 74 years. The proportion of women was higher in these trials than in other trials in heart failure. Of the patients in our analysis 39% were women, as compared to 26% in the SOLVD registry [1,2]. The mean ejection fraction of patients was 46% which is higher than other published studies [1–3]. The mean end-diastolic dimension was 68 mm indicating that patients enrolled had dilated ventricles.

The mechanism by which diuretics prevent death is unclear because the cause and mode of death is often not described in these trials. Differentiation between death due progressive CHF and an opportunistic arrhythmia is not possible. The data are insufficient by current standards to provide a formal evidence-base to recommend diuretics in heart failure on the basis of an impact on mortality.

Diuretics have not been tested in long-term trials evaluating survival, mainly because of ethical difficulties in enrolling patients with symptoms who would benefit from these agents. In contrast, in older patients with hypertension, diuretics have been investigated in long-term prospective placebo-controlled trials, such as the Systolic Hypertension in the Elderly Program (SHEP) [34], the Swedish Trial in Old Patients with Hypertension (STOP) [35], and the Medical Research Council (MRC) study [36]. In all three studies, active treatment either diuretics alone, or combined with β-blockers, was found to be significantly beneficial in reducing mortality and morbidity.

RALES was the largest study of spironolactone, an agent with diuretic properties [15]. The mechanism the benefit from spironolactone is not clearly established and could be attributed either to a synergistic diuretic action, or to a specific mechanism of aldosterone antagonism that may reduce myocardial fibrosis by blocking the effects of aldosterone on the formation of collagen [37]. Spironolactone may prevent sudden cardiac death by avoiding potassium loss and increasing myocardial uptake of norepinephrine [38]. Recently, it has been shown that spironolactone improves endothelial dysfunction, increases nitric oxide bioactivity, and inhibits vascular angiotensin I and angiotensin II in patients with heart failure [39]. Our subsidiary analysis, including RALES, provides good evidence for the use of spironolactone in patients with advanced heart failure.

The improvement in exercise capacity in heart failure patients treated with diuretics may be due to favourable haemodynamic activity of diuretics. For example diuretics reduce central filling pressures allowing improved cardiac output on exercise at a lower left ventricular pressure [20,30]. This improved long-term cardiac performance is usually accompanied by increased exercise capacity or duration.

5. Limitations

This analysis has several limitations. All randomised trials were small with inadequate statistical power to demonstrate clearly the effectiveness of the intervention in terms of reduction in morbidity and mortality rates. There was also great variability in the type of intervention, clinical characteristics of patients, assessment of severity, aetiology of heart failure, study duration, concomitant medications, outcome measures, and drop out rates. The methods of masking and assessment of outcome measures was not clearly reported in many studies. The inclusion of cross-over studies in our meta-analysis is a weakness since most methods of meta-analysis have been developed for comparison of independent groups. Other limitations such as publications bias are common to all meta-analyses, but may have a particular influence in our study since most of the trials were small. There is also heterogeneity in the mechanism of action of the loop diuretics (e.g. furosemide) and the thiazides (e.g. bendrofluazide), and dose of diuretics.

6. Conclusion

Our study provides evidence of the benefits of diuretics on mortality, progression of heart failure and exercise capacity in patients with heart failure. This evidence from trials done is not sufficient by current standards to justify widespread use of diuretics to influence clinical outcomes. On the other hand, clinical experience with diuretics in heart failure following the seminal work of Slater and Nabarro in 1958 [40], provides clinicians with the evidences of experience for continuing to use diuretics as the initial oral maintenance medication in treatment of patients with congestive heart failure. Even in the absence of data showing a clear benefit on clinical outcomes, diuretics will continue to be used routinely in the management of CHF for symptomatic relief. Whether diuretics will be the subject of future trials to evaluate effects on clinical outcomes in compensated heart failure, particularly in patients stabilised on ACE inhibitors and beta-blockers, is unlikely.

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References

[1] The Study of Left Ventricular Dysfunction Investigators. SOLVD-Prevention Trial. New Engl J Med 1992;327:685–91.
[2] The Study of Left Ventricular Dysfunction Investigators. SOLVD-Treatment Trial. New Engl J Med 1991;325:293–302.
[3] Flather MD, Yusuf S, Kober L et al. Long-term ACE inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. Lancet 2000;355:1575–81.
[4] The Cardiac Insufficiency Bisoprolol Investigators and Committees. CIBIS Study. Circulation 1994;90:1765–73.
[5] Waagstein F, Bristow MR, Swedberg K et al. The Metoprolol in Dilated Cardiomyopathy (MDC) Study. Lancet 1993;342:1441–6.
[6] Anand IS, Kalra GS, Harris P et al. Diuretics as essential and sole treatment in chronic heart failure. Cardioscience 1997;18:852–7.
[7] Baylis J, Norell M, Canepa-Anson R, Sutton G, Poole-Wilson PA. Untreated heart failure: clinical and endocrine effects of introducing diuretics. Br Heart J 1987;57:17–22.
[8] Robson AO, Ashcroft R, Kerr DN, Teasdale G. The diuretic response to furosemide, Lancet, 1964:1085–1088.
[9] Francis GS, Benedict C, Johnson DE. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without heart failure. Circulation 1990;82:1724–9.
[10] Hollifield JW, Slaton PE. Cardiac arrhythmias associated with diuretic-induced hypokalaemia and hypomagnesaemia. Proc Roy Soc Med, 1981:17–24.
[11] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of diseases. Statistical methods for rates and proportion, 2nd edition, 1981.
[12] Edbago, Furhoff AK, Gertz I. et al. Ethacrynic acid in pulmonary oedema. Lakartidningen, 64 (1967) (Suppl 4) 85–87.
[13] Haerer W, Baure U, Sultan N et al. Acute and chronic effects of a diuretic monotherapy with piretanide in congestive heart failure: a placebo-controlled trial. Cardiovasc Drugs Ther 1990;4(2):515–21.
[14] Grinstead WC, Francis MJ, Marin GF et al. Discontinuation of chronic diuretic therapy in stable congestive heart failure. Am J Cardiol 1994;73:881–6.
[15] The Randomised Aldactone Evaluation Study (the RALES study). Effect of spironolactone on morbidity and mortality in patients with severe heart failure. New Eng J Med 1999;341:709–19.
[16] Burr ML, King S, Davies HE et al. The effects of discontinuing long-term diuretic therapy in elderly. Age Ageing 1977;6:38–45.
[17] Myers MG, Weingart MR, Fisher RH, Gryfe CI, Schulman HS. Unnecessary diuretic therapy in the elderly. Age Ageing 1982;11:213–21.
[18] Sherman LG, Liang C, Baumgardner S, Chiruzi Y, Chando F. Penitanide, a potent diuretic with potassium-sparing properties, for treatment of congestive heart failure. Clin Pharmacol Ther 1986;40(5):587–94.
[19] De Jong JW, Knomerus JA, van Zutphen WM, De Bruijne GA. Short-term effect of withdrawal of diuretic drugs prescribed for mild oedema. Br Med J 1994;308:511–3.
[20] Walma EP, Hoes AW, Van Dooren C, Prins A, Van Der Does E. Withdrawal of long-term diuretic medication in elderly patients: a double-blind randomised trial. Br Med J 1997;315:464–8.
[21] Mathur BN, Pugsley SO, Powles AC, Campbell AJ, McEwan MP. Effect of diuretics on cardiovascular performance in severe chronic airflow disease. Arch Intern Med 1984;144:2154–7.
[22] Chaithin MD, Byrd R, Benowitz N, Liu R, Modin G. Amiloride improves haemodynamics in patients with congestive heart failure treated with chronic digoxin and diuretics. Cardiovas Drugs Ther 1991;5:719–26.
[23] Barr CS, Hanson J, Arnott M, Kennedy N, Struthers AD. Effects of adding spironolactone to an angiotensin-converting enzyme inhibitor in chronic heart failure secondary to coronary artery disease. Am J Cardiol 1995;76:1259–65.
[24] Boccanelli A, Zanchara E, Liberatore SM, Carboni GP, Prati PL. Addition of captopril versus increasing diuretics in moderate but deteriorating heart failure. Postgrad Med J, 1986; suppl 1:184–187.
[25] Richardson A, Bayliss J, Scriven AJ, Swan GC, Poole-Wilson PA. Double-blind comparison of captopril alone against furosemide plus amiloride in mild heart failure. Lancet, 1987; suppl 26:709–711.
[26] Ibopamine Study Group, Parker JO. The effects of oral ibopamine in patients with mild heart failure: a double-blind placebo controlled comparison to furosemide. Intern J Med 1993;40:11–9.

[27] Andrews R, Charles Worth A, Evans E, Cowley AJ. A double-blind, cross-over comparison of the effects of a loop diuretic and a dopamine receptor agonist as first line therapy in patients with mild congestive heart failure. Eur Heart J 1997;18:852–7.
[28] Cowley AJ, Steiner K, Wynn RD, Rowley IM, Hampton JR. Symptomatic assessment of patients with heart failure: double-blind comparison of increasing captopril in patients with moderate heart failure. Lancet 1986;2:770–2.
[29] Hamer W, Hetzel M, Fehske KL, Stauch M et al. The impact of digoxin and diuretics on exercise tolerance in congestive heart failure: a placebo controlled randomised double-blind trial. Circulation 1989;80:1698A.
[30] SK and F Ibopamine Working Group. Ibopamine versus hydrochlorothiazide/amiloride in chronic heart failure. Cardiovasc Drugs 1989;3(3):897–902.
[31] Dalhstrom UF, Areskog M, Wranne B, Karlsson E. Prenalterol as a long therapy for chronic congestive heart failure: a randomised cross-over trial with intensified diuretics. Acta Med Scand 1986;216(2):199–207.
[32] Sievert H, Offermann T, Kaltenbach M et al. Basic therapy of chronic heart failure with digitalis or diuretics? (abstract). Dtsch Med Wochenschr 1989;114(10):363–7.
[33] Nordrehaug JK, Omsjo IH, Vollset SE. A 3-month double-blind cross-over study of the effect of Benazepril and hydrochlorothiazide on functional class in symptomatic mild heart failure. J Intern Med 1992;231:589–94.
[34] SHEP Co-operative Research Group. Systolic hypertension in elderly program. J Am Med Assoc 1991;265:3255–64.
[35] Dahlof B, Lindholm LH, Hansson L et al. Swedish trial in old patients with hypertension (STOP-hypertension). Lancet 1991;338:1281–5.
[36] MRC Working Party. Medical research council trial of treatment of hypertension in older adults. Br Med J 1992;304:405–12.
[37] Burr CS, Nasa A, Freeman M. QT dispersion and sudden unexpected death in chronic heart failure. Lancet 1994;343:327–9.
[38] Klug D, Robert V, Swynghedauw B. Role of mechanical and hormonal factors in cardiac remodelling and biologic limits of myocardial adaptation. Am J Cardiol 1993;71(Suppl A):46–54.
[39] Farquharson CA, Struthers AD. Spironolactone increases nitric oxide bioactivity, improves endothelial vasodilator dysfunction, and suppresses vascular angiotensin I/angiotensin I I conversion in patients with chronic heart failure. Circulation 2000;101(6):594–7.
[40] Slater JDH, Nabarro JDN. Clinical experience with chlorothiazide. Lancet 1958;1:124–6.